CENTRO INTERNACIONAL DE ESTUDOS
DE DOUTORAMENTO E AVANZADOS
DA USC (CIEDUS)

DOCTORAL THESIS

COPD AND LUNG CANCER: UNDERDIAGNOSIS AND CLINICAL CHARACTERIZATION.

Cecilia Mouronte Roibás

ESCUELA DE DOCTORADO INTERNACIONAL

PROGRAMA DE DOCTORADO EN EPIDEMIOLOGÍA Y SALUD PÚBLICA

SANTIAGO DE COMPOSTELA

2019

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COPD and lung cancer: underdiagnosis and clinical characterization.

Dña. Cecilia Mouronte Roibás.

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COPD and lung cancer: underdiagnosis and clinical characterization.

Alberto Ruano Raviña, PhD.
Alberto Fernández Villar, MD, PhD.
Virginia Leiro Fernández, MD, PhD.

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Que la presente tesis, corresponde con el trabajo realizado por Dña. Cecilia Mouronte Roibás, bajo nuestra dirección, y autorizamos su presentación, considerando que reúne los requisitos exigidos en el Reglamento de Estudios de Doctorado de la USC, y que como directores de ésta no incurre en las causas de abstención establecidas en Ley 40/2015.

Además, la presente tesis es idónea para ser presentada de acuerdo con el artículo 41 del Reglamento de Estudios de Doctorado de la USC, por la modalidad de compendio de ARTÍCULOS, en los que la doctoranda participó en el peso de la investigación, siendo su contribución decisiva para llevar a cabo este trabajo. Del mismo modo, esta tesis está en conocimiento de los coautores, tanto doctores como no doctores, participantes en los artículos, y ninguno de los trabajos reunidos en esta tesis serán presentados por ninguno de ellos en otra tesis doctoral, lo que firmamos bajo nuestra responsabilidad.

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That this thesis corresponds to the work done by Mrs. Cecilia Mouronte Roibás, under our direction, and authorize its presentation, considering that it meets the requirements of the Reglamento de Estudios de Doctorado de la USC, and that, as directors of this work, it does not incur in the causes of abstention established in the Law 40/2015.

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which the doctoral student participated in the the research, her contribution being decisive to carry out this work. Also, all co-authors are aware of the contents of this thesis, both doctors and non-doctors, participants in the articles, and none of the works gathered in this thesis will be presented by any of them in another doctoral thesis, which we sign under our responsibility

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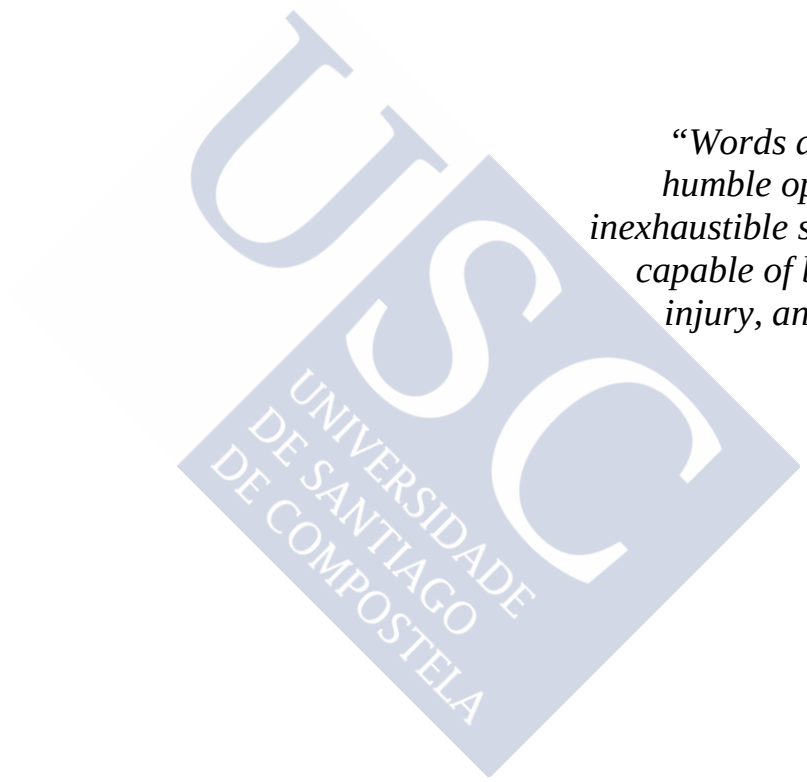

"Words are, in my not so humble opinion, our most inexhaustible source of magic, capable of both influencing injury, and remedying it"

J.K. Rowling.

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Special thanks:

To Alberto Ruano, my thesis director, for his help and advice, as well as for his permanent availability and his constructive opinions, which have been essential for the conclusion of this thesis.

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To my friends: Luís, Andrea and Dani, Naty and Sisqo, Adrián and Gary, Pablo and Marta and Maik, for all the shared moments, for their patience and for their trust and joy shared by each of the successes achieved, even from a distance. To Lourdes, wherever you are, for always reminding me "a que me atreva con las ocho".

To my parents, for providing me with the best values and education. Also, for showing me that efforts are worthwhile, and for showing me how to become a hard-working, independent woman with my own criteria. I especially appreciate the effort to help me to become a physician, even in times when it did not seem easy. Thank you.

To my grandparents, for believing their granddaughter is capable of "the impossible". Sara, for her interest on her cousin's job, being still so young. To Marga and Luis, and to the rest of my in-laws, for welcoming me as one of them from the beginning.

To David, my husband, for loving me, for sharing his life with me, for his priceless advice, for always being an example of patience and overcoming, for believing in me and, above all, for his unconditional support in all my projects, regardless of how complex and absorbing they may be.

To the patients who participated in the studies. Thank you for trusting this team. This thesis has been carried out for them.

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PRESENTATION

Lung cancer (LC) is the leading cause of cancer death in the world and is currently the most diagnosed neoplasm. In Spain, there were 28,645 new cases of cancer (more than 80% in men) in 2017. Chronic Obstructive Pulmonary Disease (COPD) is the fourth cause of death in the world, and it is estimated that it will be the third by 2020. COPD prevalence is around a 10%, although there is a high rate of underdiagnosis in general population. Many patients who smoke and, in particular, patients with COPD have pulmonary emphysema. Emphysema is a pathological lesion defined by the dilation of distal airways accompanied by their wall destruction. COPD prevalence in patients with LC has shown to be very variable among studies, ranging between 8 and 50%. Both diseases share smoking as a risk factor, in addition to other common pathogenic characteristics. It also seems that COPD may be a risk factor for LC development, independent of tobacco consumption. On the other hand, certain blood circulating molecules have been associated in COPD with higher mortality and exacerbations, and in cancer with a higher risk of malignancy, worse prognosis and worse response to treatment. In addition, there are data suggesting that the presence of emphysema increases the risk of developing LC, which reinforces the pathogenic relationship between COPD and LC. However, the role of emphysema in the relationship between the two diseases is not very clear.

Despite of the existence of the mentioned associations, to date, information on whether patients with COPD and LC have any differential characteristics when compared to patients with COPD without LC that can explain an increase in carcinogenic susceptibility is lacking. There are no studies that analyze differences in their phenotypic characterization, multidimensional aspects or comorbidities, issues that are important for COPD phenotyping, as well as in the choice of targeted therapies and in the prognostic stratification of LC. It is also unknown how tumor stage impacts on COPD itself. On the other hand, although there are several types of emphysema, few studies have evaluated the relationship between each type and the risk of LC.

According to the evidence on the potential association between COPD and LC (with or without emphysema), an investigation that allows to know epidemiological and clinical data has been carried out, in order to better characterize the interaction between both diseases. COPD prevalence and underdiagnosis in LC patients, and the profile of patients with COPD and LC were determined, comparing it with a control group of patients with COPD without LC, analyzing its phenotypic and multidimensional characterization. The finding of differential

aspects could have a potential utility in LC screening in COPD patients, in LC early diagnosis, or even prognostic utility, being helpful in the treatment decision making process.

This thesis is part of the project "COPD and lung cancer, underdiagnosis and clinical characterization" (110/2016) endorsed and funded by the *Sociedad Española de Patología Respiratoria* (SEPAR), and has been developed with the following aims:

1. To estimate COPD prevalence among patients with LC diagnosis, as well as the proportion of previously undiagnosed patients in whom COPD is detected in the spirometry performed at the time of LC evaluation.
2. To assess the differential clinical characteristics of patients with LC with or without concomitant COPD.
3. To evaluate the clinical profile of patients with COPD and LC, comparing it with a control group of patients with COPD without LC, in order to stablish their phenotypic and multidimensional characterization.
4. To search for blood inflammation markers with potential diagnostic, prognostic and therapeutic utility, with the objective of modifying future approaches to LC screening strategies.

This work is structured in ten chapters. The introduction reviews the available evidence regarding the epidemiology of LC and COPD, as well as any risk factors that have been related to both diseases. In addition, a review of the available data on epidemiological and radiological characteristics of emphysema has been made. The second chapter presents the main and specific objectives proposed in this investigation. The third chapter refers to the characteristics of the subjects included in the studies, as well as the methods used for the development of this work. The following five chapters correspond to the results, showing four articles already published or pending publication in which, the results of this research are collected and analyzed. The first article is a systematic review of the articles published to date on the relationship between COPD, emphysema and LC. The second article shows the results of a multicenter study evaluating differential characteristics of COPD patients in a cohort of patients with LC diagnosis, whereas the third article presents with the results of a case-control study comparing cases with COPD and LC with a control group of COPD without LC. The fourth article is a case-control study comparing 16 biomarker levels in a group of cases with COPD and LC and two control groups: COPD without LC and LC without COPD.

The aim of the cohort study is to estimate the prevalence and degree of underdiagnosis of COPD among patients with LC diagnosis, in addition to evaluating differential clinical characteristics of patients with LC and COPD and patients with LC without COPD. The aim of the case-control studies is to determine the clinical, radiological and biochemical profile of patients with COPD and LC, comparing it with another control group of patients with COPD without LC, to analyze its phenotypic and multidimensional characterization, to evaluate a possible relationship between a specific type of emphysema and the existence of LC in patients with COPD and to establish whether differential levels of blood biomarkers can predict which patients belong to the LC and COPD group.

The penultimate chapter includes the discussion, which reflects the method and results obtained in this doctoral thesis and the last chapter reflects the conclusions of this work.

Note: this is a thesis performed by the modality of compendium of articles, in which three studies already published in international journals are presented. The first article is a systematic review published in *Cancer Letters*, a first-quartile journal, with an impact factor of 6.491 occupying position 25/217 of Oncology journals in the Journal Citation Reports. The second article has been published in *Respiration*, a second-quartile journal, which has an impact factor of 2.591 and occupies position 31/59 of the Respiratory System journals and is the official journal of the European Association for Bronchology and Interventional Pulmonology. (EABIP). The third article has been published in the *International Journal of COPD*, a second-quartile journal, with an impact factor of 2.917 and ranking 25/59 among the Respiratory System journals. The fourth article has been sent to press, currently pending acceptance.

Regarding the contribution of the doctoral candidate to the development of the published articles included in this thesis, in the case of the study "COPD, emphysema and the onset of lung cancer. A systematic review", she was responsible for carrying out the initial bibliographic search, as well as being one of the two reviewers of the aforementioned bibliography to verify that selected articles met the inclusion and exclusion criteria, she was also responsible for carrying out the data analysis, as well as the preparation of the manuscript and its submission for publication. In the article "Chronic Obstructive Pulmonary Disease in Lung Cancer Patients: Prevalence, Underdiagnosis and Clinical Characterization", the doctoral candidate took part in the data collection and analysis, in the study design, in the manuscript preparation and in its submission for publication. In the study "Influence of the type of emphysema in the relationship

between COPD and lung cancer", the doctoral candidate took part in the conception and design of the study, performed the data acquisition as well as the analysis and interpretation of the data and developed the draft article with a critical review of its content, being also responsible for its submission for publication. In the article pending publication "Predictive value of a series of inflammatory markers in COPD for lung cancer diagnosis", the doctoral student took part in the choice of markers, in the selection of patients, in obtaining blood samples, in the analysis of the existence of emphysema, in the statistical analysis of the data, as well as in the design, elaboration, correction and sending of the manuscript.

In all the articles included in this doctoral thesis, reference is made to the absence of any conflict of interest from the doctoral candidate or from any other coauthor of the mentioned works.

The doctoral candidate has actively participated as first author in another publication, an editorial requested to our group after the publication of the first two articles included in this thesis, by the journal *Translational Lung Cancer Research*, entitled: "Lung cancer and chronic obstructive pulmonary disease: understanding the complexity of carcinogenesis ". The article is presented as an annex at the end of this thesis.

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Spanish summary (Resumen en español)

En estos años se han publicado numerosos estudios que parecen mostrar la existencia de una relación entre el cáncer de pulmón (CP), la enfermedad pulmonar obstructiva crónica (EPOC) y el enfisema. Sin embargo, no existen estudios de caracterización fenotípica y multidimensional de los casos de EPOC con CP que nos puedan ayudar a elegir la terapia más adecuada y su pronóstico. Tampoco se ha estudiado la posibilidad de una relación entre distintos tipos de enfisema y la existencia de CP. Del mismo modo, existe escasa evidencia acerca del papel que representan algunos marcadores de inflamación en sangre, que podrían servir como herramientas de diagnóstico precoz, de posible cribado del CP, de determinación de gravedad, de evaluación de respuesta terapéutica y/o de toma de decisiones diagnósticas y terapéuticas en el subgrupo de pacientes con una EPOC de base. El objetivo de esta tesis es estimar la prevalencia de EPOC y su grado de infradiagnóstico en pacientes con CP, así como evaluar el perfil clínico de pacientes con EPOC y CP y compararlo con otro grupo control de pacientes con EPOC sin CP, para analizar su caracterización fenotípica, radiológica y multidimensional, teniendo en cuenta la poca literatura existente y sus resultados discrepantes.

Los dos hallazgos más novedosos alcanzados en los trabajos que incluye esta tesis son que el enfisema paraseptal en pacientes con EPOC es más frecuente en el subgrupo de pacientes que además presentan CP, especialmente dentro del subgrupo de los adenocarcinomas, y que los niveles elevados de alfa-1 antitripsina y de neutrófilos y los disminuidos de colesterol, se asocian con una mayor probabilidad de presentar un CP en pacientes con EPOC. De hecho, el estudio de los biomarcadores nos ha permitido desarrollar una escala de riesgo que ha mostrado una elevada sensibilidad y valor predictivo negativo, con un área bajo la curva (AUC) cercana a 0,80.

Teniendo en cuenta estos resultados sobre el enfisema paraseptal y los biomarcadores sanguíneos, este proyecto se intentará continuar con varios trabajos multicéntricos a nivel nacional. Estos estudios se diseñarán para validar prospectivamente nuestros resultados, con el objetivo de poder plantear una escala combinada de parámetros clínicos, exposiciones de riesgo, función pulmonar, tipo de enfisema y marcadores en sangre, que permita seleccionar a aquellos pacientes con EPOC susceptibles de ser la población diana en estrategias de cribado de CP. Como objetivo secundario, se pretende modificar las escalas predictoras de malignidad en el estudio de nódulos pulmonares y otras lesiones sospechosas de CP en pacientes con EPOC.

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Glossary of abbreviations

95%CI: 95% confidence interval

A1AT: Alpha-1 antitripsin

AATD: Alpha-1 antitripsin deficiency

AECC: Asociación Española Contra el Cáncer

AJCC: American Joint Committee on Cancer

ALK: Anaplasic lymphoma kinase

ATS: American Thoracic Society

BMI: Body mass index

BOLD: Burden of Obstructive Lung Diseases

CAT: COPD assessment test

COPD: Chronic obstructive pulmonary disease

CRP: C reactive protein

CT: Computed tomography

CTLA4: Lymphocyte-T associated antigen 4

DALY: Disability-adjusted life year

DL: Detection limit

DLCO: Carbon monoxide difussion capacity

DNA: Deoxyribonucleic acid

EBUS: Endobronchial ultrasound

EGF: Epidermal growth factor

EGFR: Epidermal growth factor receptor

EPA: Environmental Protection Agency

ERS: European Respiratory Society

ESCAPE: European Study of Cohorts for Air Pollution Effects

FEV_1: Forced expiratory volume in the first second

FVC: Forced vital capacity

GesEPOC: Guía Española de la EPOC

GOLD: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease

HDAC: Histones

HR: Hazard ratio

IARC: International Agency for Research on Cancer

IASLC: International Association for the Study of Lung Cancer

IgE: Immunoglobulin E

IL: Interleukin

INE: Instituto nacional de estadística

INL: Inferior normality limit

KCO: Carbon monoxide transfer coefficient

LC: Lung cancer

LCRDU: Lung cancer rapid diagnosis unit

LLN: lower limit of normality

MPV: Mean platelet volume

MRC: Medical Research Council

NETT: National Emphysema Treatment Trial

NLR: Neutrophil/lymphocyte ratio

NPV: Negative predictive value

NSCLC: Non-small cell lung cancer

OR: Odds ratio

PD1: Programmed death protein type-1

PII: Programa integrado de investigación

PLATINO: Latin American Project for the Investigation of Obstructive Pulmonary Disease

PLR: Platelet/lymphocyte ratio

PM: Suspended particles

PPV: Positive predictive value

RNA: Ribonucleic acid

SBRT: Stereotactic body radiation

SCLC: Small cell lung cancer

SEER: Surveillance, Epidemiology and End Results program

SEOM: Sociedad Española de Oncología Médica

SEPAR: Sociedad Española de Patología Respiratoria.

SNS: Sistema Nacional de Salud

TGF-β: Beta transforming growth factor

TNF-α: Tumor necrosis factor alpha

TNM: Tumor, node, metastasis

UICC: Union Internationale Contre le Cancer

USA: United States of America

VEGF: Vascular endothelial growth factor

WHO: World health organization

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Index of the publications includes in this thesis:

All the publications included in this thesis reflect that they are part of it.

1. **Mouronte-Roibás C**, Leiro-Fernández V, Fernández-Villar A, Botana-Rial M, Ramos-Hernández C, Ruano-Ravina A. COPD, emphysema and the onset of lung cancer. A systematic review. Cancer Letters. 2016 Nov 28;382(2):240-244. http://www.cancerletters.info/article/S0304-3835(16)30544-4/fulltext
2. **Mouronte-Roibás C**, Leiro-Fernández V, Ruano-Raviña A, Ramos-Hernández C, Abal-Arca J, Parente-Lamelas I, Botana-Rial M, Priegue-Carrera A, Fernández-Villar A. Chronic Obstructive Pulmonary Disease in Lung Cancer Patients: Prevalence, Underdiagnosis and Clinical Characterization. Respiration. 2018;95(6):414-421. https://www.karger.com/Article/Pdf/487243
3. **Mouronte-Roibás C**, Fernández-Villar A, Ruano-Raviña A, Ramos-Hernández C, Tilve-Gómez A, Rodríguez-Fernández P, Caldera Díaz AC, García Vázquez-Noguerol M, Fernández-García S, Leiro-Fernández, V. Influence of the type of emphysema in the relationship between COPD and lung cancer. International Journal of COPD. 2018;13:3563-3570.
   https://www.dovepress.com/articles.php?article_id=41849
4. **Mouronte-Roibás C**, Leiro-Fernández V, Ruano-Raviña A, Ramos-Hernández C, Casado-Rey P, Botana-Rial M, García-Rodríguez E; Fernández-Villar A. Predictive value of a series of inflammatory markers in COPD for lung cancer diagnosis.
   Publication pending.

Annex 4

1. **Mouronte-Roibás C**, Ruano-Raviña A, Fernández-Villar A. Lung cancer and chronic obstructive pulmonary disease: understanding the complexity of carcinogenesis. Transl Lung Cancer Res 2018. doi: 10.21037/tlcr.2018.08.11
   http://dx.doi.org/10.21037/tlcr.2018.08.11

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CHAPTER 1.

INTRODUCTION

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1.1. Lung Cancer Epidemiology.

Lung cancer (LC) represents about 13.5% of all tumors, being almost the most frequent worldwide, exceeded only by breast cancer, and it is the third cancer after colorectal and prostate cancer in Spain (1-4). Its survival at 5 years slightly exceeds 18%, being surgery the most favorable treatment in early stages, achieving a five-year survival of around 60% for stages I and II (3,5).

1.1.1. LC incidence.

The most recent data on LC incidence worldwide are obtained through the World Health Organization (WHO) refer to the year 2012, whereas data from the International Agency for Research on Cancer (IARC, Globocan) refer to the year 2018, in which 2.1 million new cases of LC in the world were diagnosed (2,6). However, we have national and international statistics that allow us to estimate the impact of this disease. According to the Surveillance, Epidemiology and End Results Program (SEER), in 2018 there were 234,030 new cases only in the United States (USA) (3).

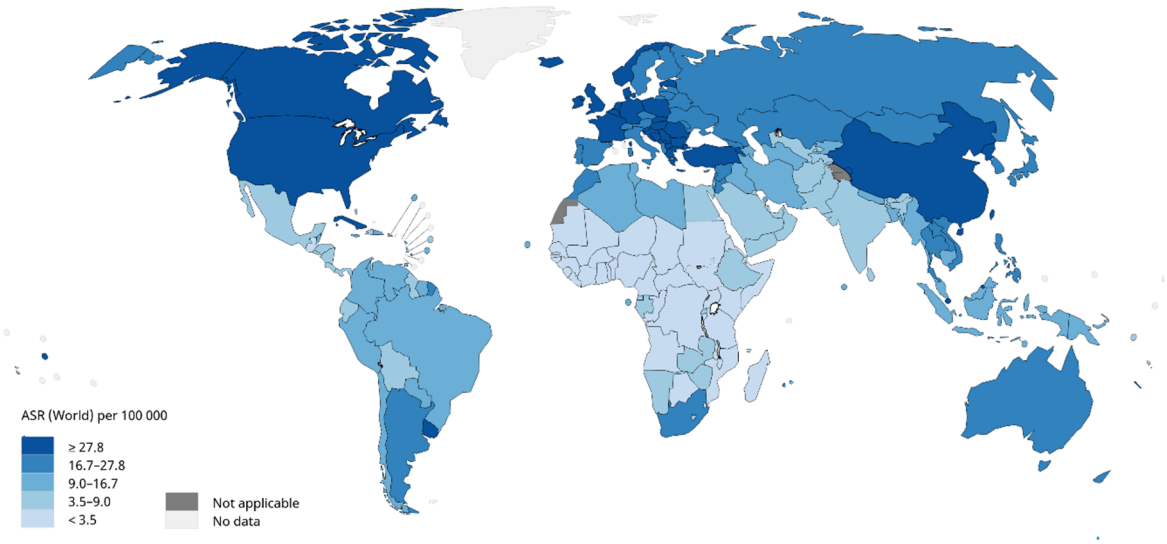

Figure 1. LC incidence rates in the world in 2018 for both sexes. Source: International Agency for Research on Cancer (IARC). Globocan 2018. Permitted by The International Agency for Research on Cancer (IARC).

In Spain, in 2017 there were 28,645 new cases of LC (81.5% in men and 18.5% in women, according to data from the *Asociación Española Contra el Cáncer* (AECC) and the *Sociedad*

Española de Oncología Médica (SEOM). In addition, although in recent years there has been a trend towards incidence stabilization in men, an increase in women is being observed (4,7,8).

1.1.2. LC mortality.

As previously stated, LC limits survival, which currently stands around 15% for all LCs, and around 18.1% for non-small cell lung cancer (NSCLC), which is the group representing 80% of all LCs (3). Unfortunately, despite important advances in diagnostic and therapeutic techniques, survival rates have changed very little in recent decades (9-11). The high mortality derived from LC is the result of a high proportion of diagnoses in advanced stages, being possible to identify tumors in localized stages only in 16-22% of cases. On a positive note, several series report an increase in localized stages of LC at diagnosis, due to the existence of new diagnostic techniques, the easier access to them and the implementation of rapid diagnostic units (3, 12). In these cases, survival can reach up to 56.3% at 5 years (12).

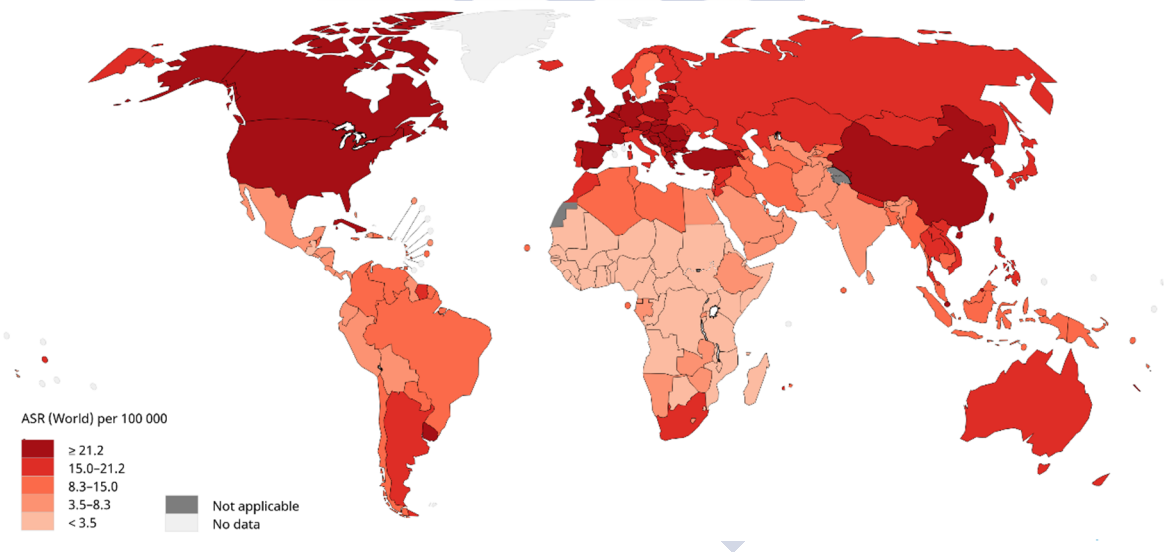

Figure 2. Mortality rates of LC worldwide in 2018 for both sexes. Source: International Agency for Research on Cancer (IARC). Globocan 2018. Permitted by The International Agency for Research on Cancer (IARC).

Mortality rates vary widely between different countries, as LC is a disease in which mortality is directly proportional to the tobacco history of each country (10). In the USA, according to data from the SEER, in 2018 there were 154,050 deaths by LC (3). In our country, according to data from the *Instituto Nacional de Estadística* (INE), in 2016, 22,187 inhabitants died because of LC (17,424 men and 4,563 women) (13), with a global mortality of 19.4%, thus representing the cancer with the highest mortality in Spain (14).

1.1.3. Sex and age.

LC is the most frecuent neoplasm causing mortality in men, being the third most common cause of death in women (13,15). The pattern of tobacco consumption in both men and women has changed in recent decades, leading to changes in the incidence rates of LC by sex, which have increased more in women than men in recent years. Nevertheless, LC is still a more frequent disease in men (15) and, in fact, in our country the male/female relationship is still high (4:1), although it is lower than it was two decades ago (10:1) (16,17). Cancers with higher mortality stratified by sex are LC and colorectal in males and breast and colorectal in women (14).

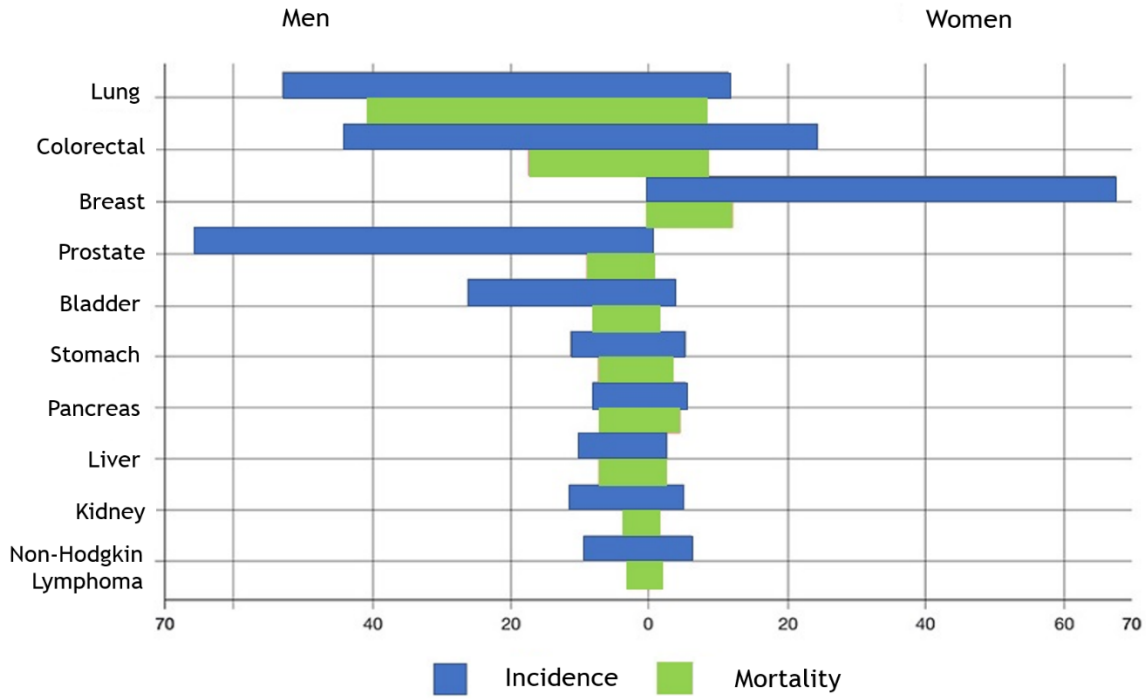

Figure 3. Causes of cancer by sex in Spain in 2012: incidence and mortality. Figure of my own elaboration made from the data published in the source: International Agency for Research on Cancer (IARC). Globocan 2012.

Due, in part, to the relationship of LC with smoking, and to the existence of a latency time between tobacco consumption and the development of disease, LC usually presents at 65-74 years, with a median age of 70 years at diagnosis (3). In Spain, the proportion of patients older than 70 years with newly diagnosed LC is greater than 50% (9). On the other hand, the incidence falls after 80 years, an age with a lower prevalence of smoking, in which there may be a survival bias derived from the existence of some type of genetic resistance to certain risk factors. The median age of patients dying from LC is 72 years (3,16).

1.1.4. Histological type, molecular characterization and immunotherapy.

Most LC consist on non-small cell lung cancer (NSCLC), representing an 80% of the whole, being the most frequent histological types squamous cell carcinoma and adenocarcinoma, which together account for a 60% (9). Until two decades ago, squamous carcinoma was the most frequent type, although in recent years its incidence has fallen in favor of adenocarcinoma (5,12). This may be due to different causes, such as changes in the classification of adenocarcinoma (the *International Association for the Study of Lung Cancer* [IASLC], the *American Thoracic Society* [ATS] and the *European Respiratory Society* [ERS] reclassified bronchio-alveolar as adenocarcinoma) or to the increase of casual diagnoses due to advances in radiodiagnosis, which allow the diagnosis of more peripheral tumors that produce symptoms later, as in the case of adenocarcinoma. It may also be due to changes in the characteristics of cigarettes (with filter and lower nicotine levels) and the increase in women with LC, a fact that could be caused by a greater susceptibility derived from genetic, hormonal, and mutational factors, being, in fact, a group with higher risk of mutations in the epidermal growth factor receptor (EGFR) (17-20).

Within the remaining 20% of LC, slightly less than 10% are large cell carcinomas, whose systemic treatments are similar to those of NSCLC (21). Small cell lung cancer (or "small cell" cancer, SCLC) accounts for about 15% of thoracic tumors. They are neoplasms with an unfavorable prognosis (less than 20 months of survival in more localized stages) and in which there have been fewer therapeutic advances (22).

Although the histological type and staging of LC are still essential elements when deciding the best treatment for LC, the arrival of treatments directed to certain mutations, especially tyrosine kinase inhibitors, make it essential to perform a molecular characterization of NSCLC. EGFR is present in 10-15% of all NSCLC, and it is more frequently found in women, never smokers and Asians (23,24). Patients with mutations in oncogenes such as EGFR, ALK (anaplastic lymphoma kinase), ROS1, K-ras or MET, can be treated with targeted therapy and generally have a significantly better prognosis than the rest of patients (23-25) . Most of the treatments available to date target EGFR and ALK mutations.

Also, in recent years, much progress has been made in the detection of key points in which the tumor is able to evade the immune response. The research focuses on the study of two inhibitory receptors, such as antigen 4 associated with T lymphocytes (CTLA4) and

programmed cell death protein type 1 (PD1), with promising results with treatments such as Nivolumab or Pembrolizumab (26).

1.1.5. Staging.

LC staging is based on a nomenclature of the extension of the tumor, which supposes a uniform language throughout the world, allowing to define the stage of a specific patient and also that of cohorts of patients belonging to clinical studies, allowing us to make judgments about the best staging, diagnosis and treatment strategies for each patient. It is a system that is reviewed and updated periodically, the latest version being the 8th edition of the TNM (tumor, node, metastasis) made by the *Union Internationale Contre le Cancer* (UICC) and the *American Joint Committee on Cancer* (AJCC). This classification is valid for both NSCLC and SCLC, although it is true that the latter can also be classified as localized or extensive disease depending on whether the lesions may be covered in a single radiotherapy field (27).

Table 1. Definition of T, N and M descriptors (Adapted from Detterbeck et al. Chest 2017;151:193-203).

T (primary tumor)	**Description**
T0	No primary tumor
Tis	Carcinoma in situ (squamous or adenocarcinoma)
T1	Tumor ≤3 cm,
T1a (mi)	Minimally invasive adenocarcinoma
T1a	Tumor limited to the airways' surface
T1a	Tumor ≤1 cm
T1b	Tumor >1 but ≤2 cm
T1c	Tumor >2 but ≤3 cm
T2	Tumor >3 but ≤5 cm or affecting visceral pleura, main bronchus or hilar atelectasis
T2a	Tumor >3 but ≤4 cm
T2b	Tumor >4 but ≤5 cm
T3	Tumor>5 but ≤7 cm or invading thoracic wall, pericardium, phrenic nerve, or other nodule(s) in the same lobe
T4	Tumor >7 cm or invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus or spine; or other nodule(s) in another ipsilateral lobe
N (nodes)	
N0	No regional nodes affected
N1	Ipsilateral or hilar node metastases
N2	Ipsilateral mediastinal or subcarinal node metastases
N3	Contralateral mediastinal or hilar node metastases, or supraclavicular
M (metastases)	
M0	No distant metastases
M1a	Pleural or pericardial nodule(s) or malignant effusion, or nodule(s) in a contralateral lobe
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastasis (in one or more locations)

The description of the anatomical extension of the tumor consists of three components: T for the extension of the primary tumor, N for node involvement and M for distant metastases. Each of the three components is divided into different categories, with several descriptors that define what is included in each of them, as can be seen in table 1. Subsequently, the specific combinations of the categories T, N and M are grouped into stages, as can be seen in Table 2.

Table 2. TNM stages according to the 8th edition (Adapted from Detterbeck et al. Chest 2017;151:193-203).

T/M	Descriptor	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

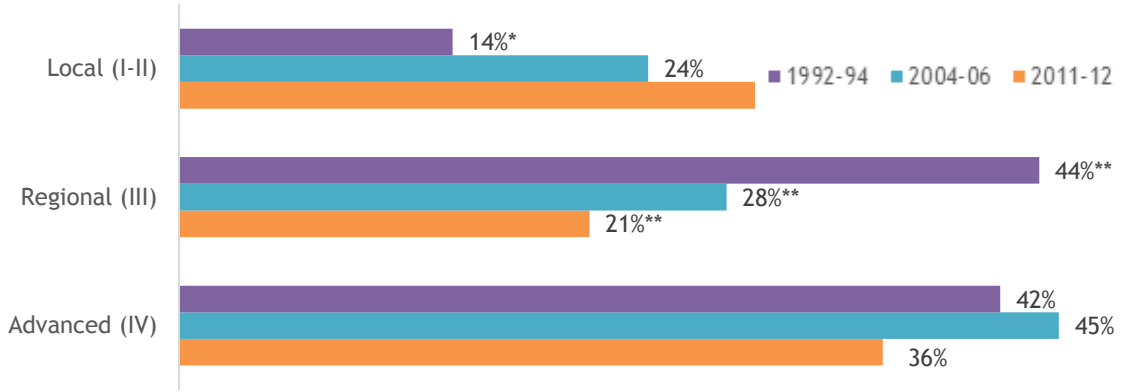

Figure 4. Changes in LC stage at diagnosis in two decades. Figure of my own elaboration made from the data published in the source: Leiro-Fernández et al. Arch Bronconeumol. 2014;50:417-21). Data correspond to percentages; *p<0.001; #p<0.001;**p<0.05..

Although LC is still a disease with a poor prognosis, more and more patients are diagnosed at more localized stages. This may be due to different reasons: diagnosis in asymptomatic patients is increasing, due to the development of better imaging techniques and easier access to them, and because it is increasingly common for other pathologies to require image follow-up,

thus casually diagnosing LC. In addition, in many centers, rapid diagnosis units and radiologist notification systems have been implemented for pulmonologists in the presence of suspicious thoracic studies. Also, mediastinal staging has been significantly improved with new, minimally invasive techniques such as endobronchial ultrasound (EBUS), which has diminished the number of patients diagnosed with metastatic lymph node involvement based solely on imaging studies (3,12,16).

1.2. Chronic Obstructive Pulmonary Disease (COPD) Epidemiology.

COPD is a respiratory disease characterized by a chronic airflow limitation that is not completely reversible (28). It usually presents with dyspnea and its course is progressive. Its main etiological factor is tobacco exposure, although we know that it can also be produced by exposure to other harmful particles or gases (28,29). According to its definition, to reach a COPD diagnosis it will be necessary to establish the existence of an exposure and also an obstructive spirometry (forced expiratory volume in the first second [FEV_1]/forced vital capacity [FVC] ratio <0.7 or lower than the lower limit of normality-LLN) without reversibility after performing a bronchodilator test (28,29). This is of paramount importance, given that available epidemiological data on the incidence, prevalence, morbidity and mortality, underdiagnosis and impact of COPD are highly variable, since there are works in which these criteria have not been strictly complied with.

1.2.1. COPD incidence and prevalence

COPD incidence and prevalence are variable between countries and between geographical areas within them. This is mainly due to a variability in risk exposures in each region (30,31). In general, COPD prevalence is closely linked to smoking prevalence, although in many countries, environmental, occupational exposures and fuels used for cooking and/or heating also play a very important role (32,33).

COPD prevalence is expected to increase in the coming decades, due to the continued exposure to risk factors and the aging of the population, given that, as longevity increases, more subjects may present the long-term effects of different risk factors (34).

A systematic review and meta-analysis performed between 1990 and 2004, including studies conducted in 28 countries, concluded that the prevalence of COPD is higher in smokers

and former smokers, when compared with never smokers. It is also superior in patients over 40 years of age with respect to younger patients, and also higher in men than in women (35). In the study *The Global Burden of Disease* published in 1996, the WHO estimated the global prevalence rates of COPD in 1990 at 9.3/1,000 inhabitants in men and 7.3 cases/1,000 inhabitants in women (36).

The *Latin American Project for the Investigation of Obstructive Pulmonary Disease* (PLATINO) (37) examined the prevalence of airflow obstruction after a bronchodilator test in patients older than 40 years in a main city of 5 countries in Latin America (Brazil, Chile, Mexico, Uruguay and Venezuela). In each country, it increased progressively with age, reaching the highest values in patients older than 60 years. The prevalence in the global population was very variable, from 7.8% in Mexico City (Mexico) to 19.7% in Montevideo (Uruguay). In all cases, it was higher in males (37).

The *Burden of Obstructive Lung Diseases* (BOLD) program, carried out in 29 countries, showed a prevalence of COPD grade 2 (or higher) of 10.1% (11.8% in males and 8.5% in females), with a prevalence of 3-11% among never smokers (38).

It is estimated that the number of cases of COPD worldwide in 2010 was 384 million, with an overall prevalence of 11.7% (95% confidence interval [95%CI] 8.4-15%). With an increasing prevalence of smoking in developing countries and an increasing longevity in developed countries, it is expected that the prevalence of COPD will continue to increase in the next 30 years (39).

In Spain, the first national study to measure the prevalence of COPD was the IBERPOC study, which also determined the variation in the distribution of COPD in 7 geographical areas. At that time, COPD diagnosis was established according to the definition of the European Respiratory Society as post-bronchodilator FEV_1/FVC ratio <88% in men and <89% in women. The overall prevalence was 10.6% and, when stratifying according to smoking history, it was 15% in smokers, 12.8% in former smokers and 4.1% in never smokers. This study found very important differences according to the geographical area (a prevalence of 4.9% in Cáceres and 18% in Manlleu, Barcelona), possibly due to variations in the risk factors in each region (40).

Later, in our country, the EPI-SCAN study was carried out, with the participation of Barcelona, Burgos, Córdoba, Huesca, Madrid, Oviedo, Seville, Requena (Valencia), Vic

(Barcelona) and Vigo (Pontevedra). COPD prevalence (defined on this occasion by a FEV_1/FVC <0.70 postbronchodilator) was 10.2% (15.1% in men and 5.7% in women) (41).

1.2.2. COPD underdiagnosis.

Studies on the prevalence of COPD show that there is a high degree of underdiagnosis of this disease. Despite the fact that clinical practice guidelines have been published both nationally and internationally in recent decades, underdiagnosis remains high, leading to a diagnosis of the disease in more advanced stages in which therapeutic interventions will have a lower impact, with unfavorable prognostic implications for patients (29,42).

In the IBERPOC study, 78.2% of the cases confirmed by spirometry had no previous diagnosis of COPD (40). In the EPI-SCAN study, a marked reduction in underdiagnosis was observed with respect to the IBERPOC study, reaching 73%. Also, there was a marked reduction in undertreatment, from 81% to 54% (p <0.05) (41).

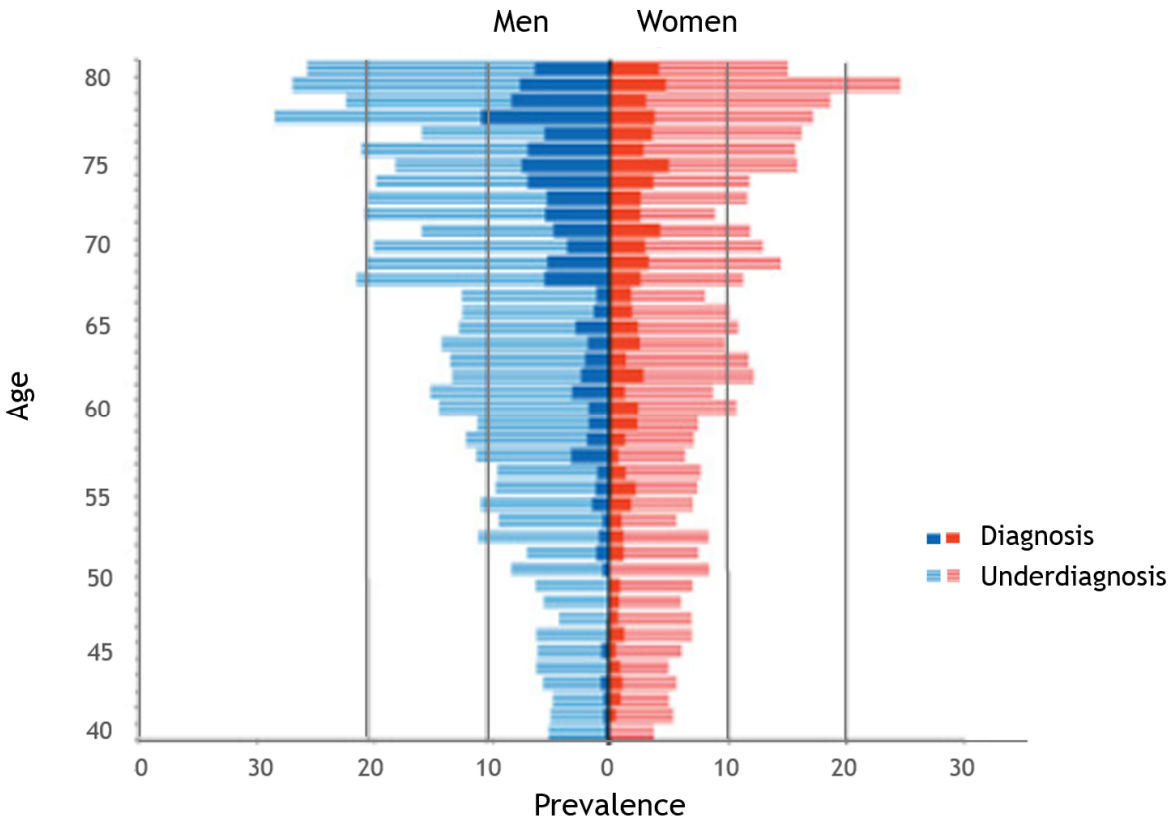

Figure 5. Prevalence of COPD diagnosis and underdiagnosis by sex and age. (Source: Adapted from Bernd et al. Chest. 2015;148:971-85). Permitted by Elsevier.

Considering the results of the EPI-SCAN, according to the calculated prevalence, 2,185,764 Spaniards aged between 40 and 80 years would have COPD (1,571,868 men and 628,102 women). However, taking into account that 73% are still not diagnosed, more than 1,595,000 Spaniards still do not know that they have the disease and also do not receive any specific treatment for it (41). Currently, the new EPI-SCAN II study is developing, and it will provide more up-to-date information on the prevalence and underdiagnosis of this disease in Spain.

1.2.3. COPD impact.

1.2.3.1. Mortality

COPD is the fourth cause of death in the world and, just as the prevalence is expected to increase in the next 30 years, the same will occur with mortality, which is why the WHO estimates that in 2030 it will be the third cause of death worldwide, with more than 4.5 million deaths per year due to COPD and its complications (43). However, we know that COPD is one of the most important causes of death already, being the third one in the USA. (44)

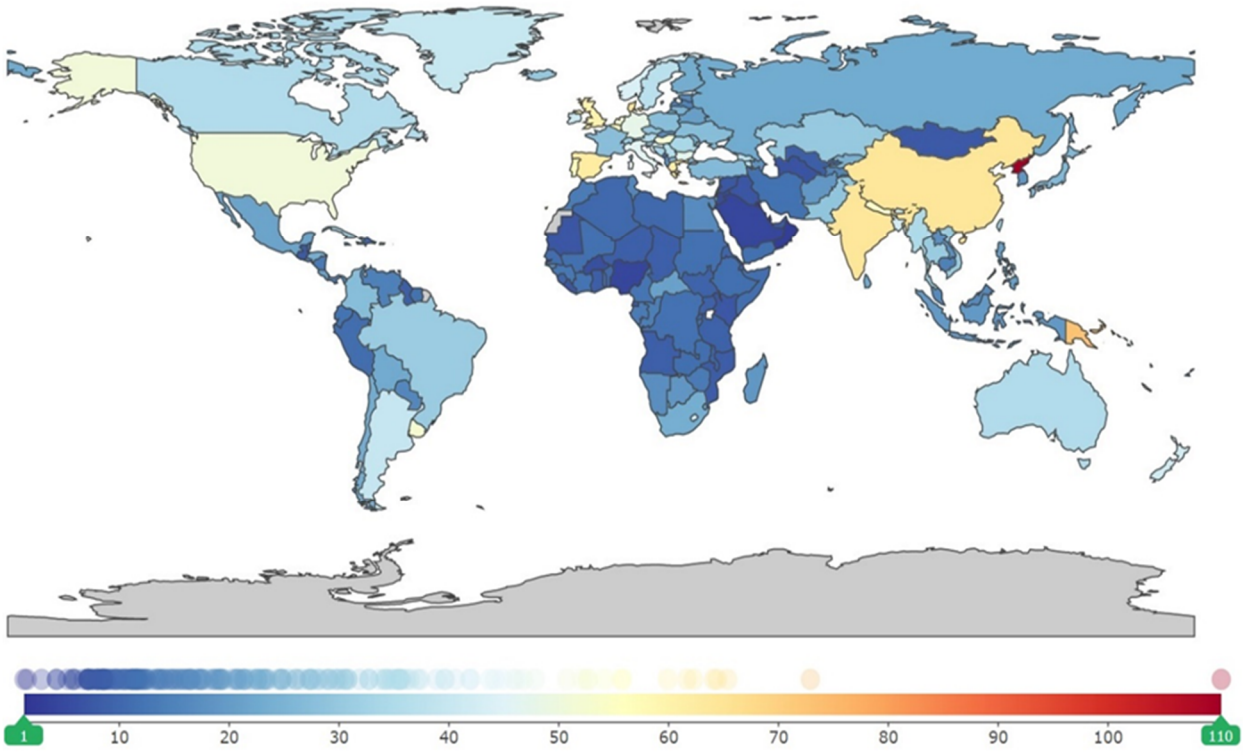

Figure 6. COPD deaths per 100,000 inhabitants, for both sexes and all ages, year 2016. (Source: Adapted from the Global Burden of Disease). Creative Commons Licence.

In 2008, chronic diseases of the lower respiratory tract represented the fourth cause of death in Spain (11.4% of total deaths), surpassed only by cancer (26.1%), heart disease (20.8%) and cerebrovascular diseases (18.2%) (45).

According to data from the *Global Burden of Disease* in 2016, COPD accounted for 5.36% of all deaths worldwide, (5.66% [5.36-5.91%] of all deaths in men and 5.01% [4.61-5.67%] of all deaths in women) (46).

1.2.3.2. Socioeconomic impact

Given that COPD is a chronic and progressive disease, it implies a significant loss of quality of life for our patients. The DALYs (Disability-Adjusted Life Years), are the sum of years lost due to premature mortality and the years lived with disability, adjusted for the severity of it. The *Global Burden of Disease* study found that COPD is currently the fifth cause of DALYs lost worldwide and it is the second cause of loss of DALYs in the USA, surpassed only by coronary heart disease (47-49).

On the other hand, the chronicity of COPD also determines a high cost derived from the consumption of health resources, with multiple visits to consultations, emergencies and hospitalizations. In Spain, according to the *Registro de Altas de los Hospitales Generales* del Sistema Nacional de Salud (SNS) of 2010, there were 58,066 hospital discharges in relation to COPD, with an average stay of 8.25 days (45). The estimated costs reviewed in the document *Estrategia EPOC* of the SNS in Spain were of 750-1,000 million euros per year, including direct, indirect and intangible costs. The direct costs were distributed in hospital expenses (40-45%), pharmacological expenses (35-40%) and visits and diagnostic tests (15-25%) (45).

In the European Union, the total direct costs for respiratory disease account for 6% of the total budgeted for healthcare, with COPD accounting for 56% of the whole (38.6 billion euros) (50). In the USA. the estimated direct costs are 32 trillion dollars and the indirect costs are 20.4 trillion dollars, with COPD exacerbations receiving a greater percentage of the budget (51).

1.3 COPD AND LC.

1.3.1. Epidemiology

As previously discussed, both LC and COPD share a series of common characteristics, such as a high mortality, with important associated comorbidity. In addition, both diseases have a series of common risk factors such as smoking, genetic alterations, environmental exposures and inflammation (52,53).

COPD is a common comorbidity among patients with LC (54,55), with a very variable prevalence among studies, ranging between 28 and 40%, due mainly to methodological differences in COPD definition, some of them not clearly stating the difference between COPD and emphysema, and also because of the high underdiagnosis of this disease, both in patients with LC and in general population (56,57). In addition, evidence of an association between COPD and the development of LC has been observed in population studies, LC screening studies, and case-control studies (58-61).

The first studies demonstrating a relationship between COPD and LC were performed in the 1980s, when Skillrud et al. (62) and Tockman et al. (63) described an increase in the incidence and mortality of LC in patients with airflow obstruction. Several subsequent studies have confirmed this fact, with an increase of between 2 and 4 times in the risk of developing LC (60,64-67).

In a recent meta-analysis (68), a strong association was found between FEV_1 decline and LC. Compared with the highest quintile of FEV_1 (>100% of predicted), the lowest quintile (<70% of predicted) was associated with an increased risk of LC. In patients with COPD, even a small decrease in predicted FEV_1 (below 90%) showed a higher risk of developing LC [OR 2.56 (95% CI 1.29-5.07)].

COPD underdiagnosis is very high in most series, both in the general population and in patients with LC, where some studies have shown a previous diagnosis of COPD of 7.1% (69). Despite the availability of national and international guidelines, COPD remains underdiagnosed in patients with LC, which implies serious delays in diagnosis and treatment and, therefore, in the prognosis of these patients.

COPD in patients with LC may pose certain limitations when it comes to LC treatment. One of the consequences is that patients are inoperable, due to a functional limitation. In addition, COPD increases the frequency of all postoperative complications, such as pneumonia

(10.1-16.2% after surgery) (70-72), atelectasis (3.5-15.4%) (72,73) , empyema (2.2-8.3%) (71) and persistent air leak (12-16.2%) (70,74). One option in patients with surgery limitations is the SBRT (Stereotactic body radiation), which justifies once again the importance of knowing if the patient has COPD in order to decide the best option for LC treatment. There are few studies that have investigated the effect of COPD in patients with advanced forms of LC. The presence of COPD has not shown a prognosis worsening in patients with chemo or immunotherapy, nor changes in the quality of life (75).

Most studies show that COPD implies an unfavorable effect on LC prognosis (71,76,77), although some show differently (75,78). Two recent meta-analyzes indicate that COPD is an unfavorable prognostic factor, although there was a significant heterogeneity between studies included in them (79).

A prognostic model (COPD-LUCSS-DLCO) has been designed to identify patients with COPD and an increased risk of dying from LC (80). Patients were divided into two risk groups based on a score obtained from the combination of their age, body mass index (BMI), smoking and DLCO (diffusing capacity of carbon monoxide). Patients in the high-risk group were 2.4 times more likely to die than the low-risk group.

1.3.2. Common risk factors.

1.3.2.1. Tobacco

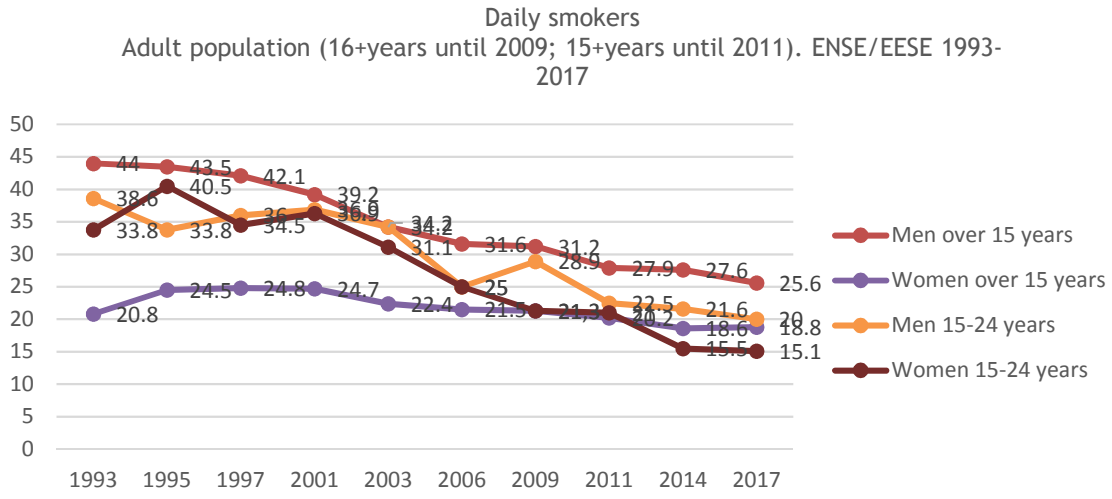

Figure 7. Figure of my own elaboration made from the data published in the source: Ministerio de Sanidad, Servicios Sociales e Igualdad. Source: EESE 2014-2017 (INE), ENSE 2003-2011 (MSSSI/INE), EES 2009 (INE/MSSSI) and ENS 1993-2001 (MSSSI).

The smoke emitted by tobacco gathers more than 4,000 different substances, with more than 60 carcinogens, such as polycyclic aromatic hydrocarbons, aromatic amines, nitrosamines (which are substances with potential capacity to irreversibly alter DNA), chloride vinyl, benzene, chromium or arsenic (81). Some of the aforementioned substances produce mutations that may persist after smoking cessation, which could partially justify the elevated risk of LC in former smokers (81).

1.3.2.1.1. Active smoking

In the last decades, multiple strategies have been developed to reduce tobacco consumption (82). However, smoking prevalence worldwide remains high. In the USA, it currently stands at 13%, and in Europe there is a greater consumption in Eastern and Southern countries, Spain being among the countries with the highest prevalence, close to 30% (81). According to the National Health Survey of 2017, 25.58% of men and 18.76% of women are active smokers, 24.93% of the Spanish population being former smokers (32.23% of men and 18.02% of women) (83). In recent years the prevalence of smoking in men has dropped, while in women the prevalence of smoking has remained stable, and the number of young people who start smoking is still high. In Spain, in 2016, the number of young people smoking increased by 50,000 when compared to 2014, most of them being over 14 years of age. There were no significant differences by sex at the beginning of the consumption. For the first time, the average age of onset of tobacco use has been delayed until 14.1 years, which implies a progressive delay of one year in the first contact with this substance, which in 2006 stood at 13.1 years, according to data from the ESTUDES 2016-2017 survey (84).

As previously mentioned, since tobacco is a risk factor for LC development, a latency time between consumption and the development of the disease is necessary. This time is estimated, on average, in 30 years. A Spanish study observed that the increase in the prevalence of smoking 32 years earlier was associated with the peak of mortality due to LC between 2006 and 2013, due to the fact that, according to surveys of the SNS, the prevalence of smoking increased a 7% between 1974 and 1981, and only 3.8% from 1981 to 1988. On the other hand, smoking in women reached its peak in the mid-90s, so that LC mortality in women is expected to continue increasing until the year 2026 (85).

The risk of developing diseases related to tobacco consumption, such as COPD or LC, depends on the latency time, but it will also be proportional to the number of cigarettes smoked, to the age of onset of smoking (with a higher risk at a younger age), to the degree of inhalation, to the amount of carcinogenic particles inhaled, or to the existence of unfiltered cigarettes, with an important cumulative effect (86). Up to 13% of patients with LC continue to smoke despite the severity of the diagnosis. This group presents several risk characteristics such as younger age, depression and living with a smoker (87).

Tobacco is a risk factor for the development of any type of LC, although its association with squamous and small cell types is still more marked (88).

Several studies have estimated that the absolute risk of developing COPD among smokers is between 25 and 30% (89). In addition, the risk is proportional to the accumulated consumption of tobacco, going from 26% in smokers of 15-30 packs a year to 51% in smokers of more than 30 packs a year (87).

1.3.2.1.2. Environmental exposure to tobacco smoke.

The information available about this exposure is variable among studies, not only because of the different patterns of tobacco consumption between countries, but also because of the difficulty in quantifying and recording it. However, in Europe, exposure to second or third-hand tobacco ranges from 8% in Sweden to 68% in Russia and Greece. Spain is in the group of countries with the highest exposure (around 50%), although strategies such as the *Ley Antitabaco* (82) help to minimize this fact.

Exposure to second or third-hand tobacco smoke causes LC in never smokers. Not only is it biologically plausible, but also, the urinary excretion of carcinogens such as nitrosamine has been demonstrated in patients exposed to environmental tobacco smoke (81,90). Several epidemiological studies show an excess risk of LC of 24% in never smokers exposed to environmental tobacco smoke, with the effects observed being dose-dependent (81,91).

Among never smokers, passive smoking is a risk factor involved in the pathogenesis of COPD (92,93). A study with more than 6,000 participants (mostly women), in which more than half claimed to be passive smokers, showed that the duration of passive smoking was directly related to the risk of developing COPD (93).

1.3.2.1.3. Electronic cigarette.

Electronic cigarettes were developed more than a decade ago and were designed to provide nicotine without the need to burn tobacco. In Europe, 7% of smokers in the countries included in the Eurobarometer (system of public surveys carried out by the European Commission) had once used the electronic cigarette, 1% of them using it regularly (94,95).

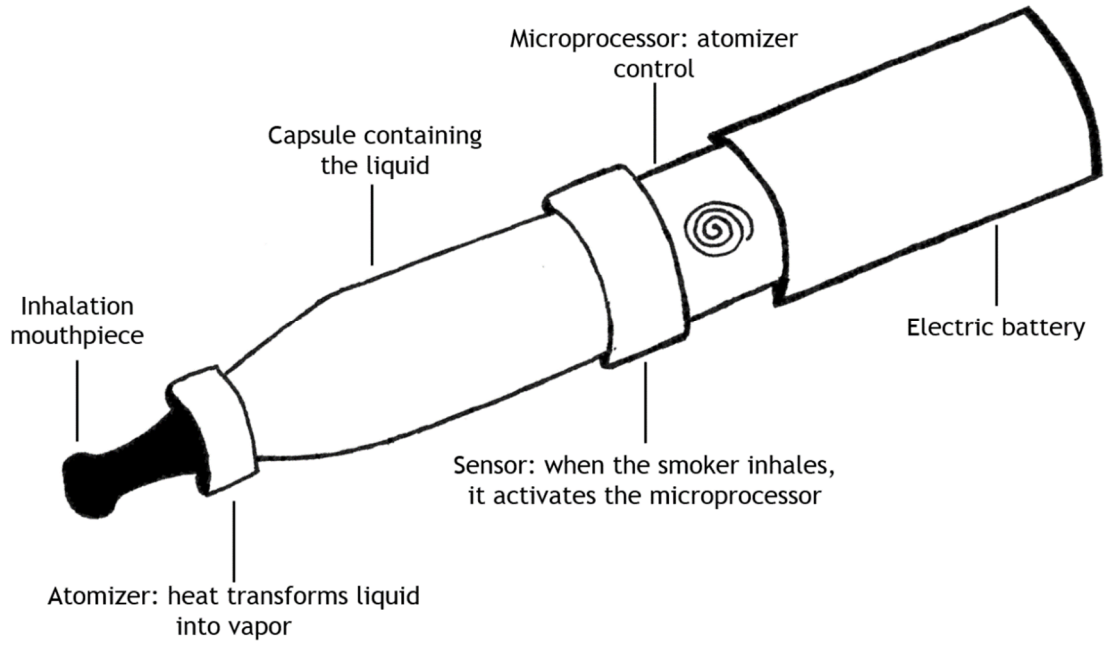

Figure 8. Electronic cigarette functioning. Figure of my own elaboration drawn from the information given by SAMHSA, VERISPAN.

With the use of electronic cigarettes, exposure to various substances occurs. The liquids contain nicotine in a glycerol or propylene glycol flavored medium. Glycerin has been linked to a case of lipoid pneumonia (94). In addition, the vapor of the electronic cigarettes contains carcinogenic substances such as formaldehyde, acetaldehyde or acroleins. It is known that electronic cigarettes provide nicotine levels similar to or even higher than those emitted by the conventional cigarette (96,97). It also contains fine particles in suspension, <2.5 microns ($PM_{2.5}$) that are harmful for both active and passive smokers (94,95).

1.3.2.2. Coal, biomass and environmental exposures.

Despite the important technological and industrial revolution that the planet has witnessed in the last century, striking socio-economic differences persist that imply that up to 40% of the

world's population is dependent on the use of biomass as fuel to meet their energy needs for cooking and heating their homes, especially in developing countries. There are several fuels of biological origin such as wood, coal, crop residues and manure (91). In several reviews, biomass and other fuels have been identified as risk factors for COPD, especially in rural areas (33,98,99). A systematic review showed that the risk of developing COPD in people exposed to biomass is 2.44 times higher than that of people who are not exposed, regardless of sex and smoking burden (100).

The IARC in 2006 classified the emissions derived from the use of fuels from biomass as 2A carcinogens (91). A case-control study conducted in Europe and the USA (101) found an increased risk of LC in people exposed to wood combustion smoke, with an OR of 1.21 (95% CI: 1.06-1.38). In addition, there could be a possible synergistic effect between tobacco and biomass (102). A meta-analysis (103) found an OR for the development of LC by exposure to biomass smoke of 1.21 (95% CI: 1.05-1.39, p=0.01) for men and 1.95 (95%CI: 1.16-1.37; p=0.01) for women.

Similarly, recent decades have been accompanied by a striking increase in environmental pollution, which includes multiple carcinogenic substances, with a potential association with the increased risk of LC in studies published in the last 50 years, although the results are heterogeneous due to large geographical differences in pollution levels (104,105). In fact, the *European Study of Cohorts for Air Pollution Effects* (ESCAPE) (106) showed a significant association between the risk of LC and PM_{10} exposure, finding an association with the histological subtype adenocarcinoma (HR 1.51; 95% CI: 1.10-2.08 for PM_{10} and HR1.55, 95%CI: 1.05-2.29 for $PM_{2.5}$).

Pollutants that have been especially linked to COPD are ozone, PM, carbon monoxide, sulfur dioxide, nitrogen dioxide and other gases. High air pollution, especially in relation to vehicles, is a trigger for COPD exacerbations in susceptible individuals. Some studies have speculated on the possible influence of internal radon exposure on COPD admissions and on the prevalence of the disease, although these data should be confirmed in more robust investigations currently underway (107).

1.3.2.3. Laboral exposure and hobbies.

LC has been related to several work-related diseases, such as silicosis or exposure to

asbestos, although it is also associated with other elements such as radon, polycyclic aromatic hydrocarbons and certain metals (cadmium, chromium and arsenic). In fact, more than 20% of workers in the European Union are exposed to carcinogens in their jobs, especially in works such as carpentry, painting, metallurgy or construction (108). In recent years, measures have been established jointly with workers and companies, aimed at limiting occupational exposure to different substances (108). However, it is estimated that, worldwide, in the year 2000, 10% of deaths from LC in men and 5% in women were attributable to 8 lung carcinogens of occupational origin: arsenic, asbestos, beryllium, cadmium, chromium, diesel fumes, nickel and silica (109).

Likewise, certain hobbies may involve exposure to certain carcinogens, often occurring for years, without the amateurs who practice them being aware of the potential risk to their lungs (110).

It is known that hobbies or occupational exposures to certain fumes can be related to a worsening of COPD, although they have not been clearly established as risk factors to develop the disease in the first place (28,29).

1.3.2.4. Diet.

There are multiple studies evaluating the influence of diet (meats, fish, fruits, vegetables and alcohol) on the risk of developing LC, with very different results. A case-control study (111) found that red meat consumption was associated with a protective effect (OR 0.24, 95%CI: 0.11-0.50), while fish consumption showed an association with the development of LC, with an OR of 1.67 (95%CI: 0.99-2.81), for both white fish and blue fish. Regarding the consumption of fruits and vegetables and the risk of LC, only a non-significant trend towards the reduction in the risk of LC was observed for green leafy vegetables and other vegetables such as potatoes (112,113).

The effect that alcohol consumption could have on the risk of developing LC is controversial. A study published in 2004 (114) observed that the consumption of red wine showed a protective effect (OR 0.43, 95%CI: 0.19-0.96), whereas there was a discrete increase in the risk associated with the consumption white wine (OR 1.20 daily for each glass consumed). Another more recent study found that the consumption of any type of wine had a relationship with LC development, with an OR of 2.2 (95%CI 1.13-3.23). In the case of beer,

the OR was 1.33 (95%CI 0.82-2.14). These results were similar when the risk for women was analyzed separately. However, in the case of men, no increase in risk was observed for any of the analyzed beverages. No dose-response pattern was found (115).

Recent evidence indicates that diet can play an important role in the development of COPD. It seems that a healthy diet based on the consumption of fruits, vegetables, cereals and fish has been associated with a lower risk of deterioration of lung function and COPD development (116,117). A cohort study conducted in Switzerland with 44,335 patients aged 45-79 years with no history of COPD at baseline found that an increase in a daily ration of fruit and vegetable consumption significantly reduced the risk of COPD by 8% among current smokers and 4% among ex-smokers (118).

1.3.2.5. Alpha-1 antitripsin.

The main activity of alpha 1 antitrypsin (A1AT), a glycoprotein encoded by the serpin 1 gene, is the inhibition of neutrophil elastase and other proteases, although several properties of this protein have been described in recent years, such as its anti-inflammatory and immunomodulatory capacity (119).

The congenital deficiency of alpha-1-antitrypsin (AATD) predisposes to an accelerated decrease in lung function (120,121). It is estimated that it is responsible for 1% of COPD cases and 2-4% of emphysema cases (120). In fact, every patient with COPD should have at least one determination of A1AT in their life (122).

Possible carcinogenic mechanisms have been proposed for which the AATD could increase the risk of LC, the majority derived from an excess in the neutrophil elastase's activity (119), which induces lung tissue damage due to a protease-antiprotease imbalance. It could also be due to the inhibition of apoptosis or the activation of matrix metalloproteases. The results of the few studies that have analyzed the possible relationship between the AATD and the risk of LC are discordant and they have biases in their design, since they include both smokers and former smokers (123-125). In a Spanish study performed in never smokers (126) a significant increase in the risk of LC in carriers of the S allele in homozygosis was demonstrated. For all these reasons, more studies are now needed to establish if there is an association between the AATD and the risk of LC.

1.3.3. Individual risk factors.

1.3.3.1. Risk factors for LC

1.3.3.1.1. Radon

The WHO classified radon as a human carcinogen in 1987 and the *Environmental Protection Agency* (EPA) in 1988. In fact, the main risk factor of environmental origin for LC development is exposure to residential radon, which represents the second cause of LC worldwide and the first one for never smokers (127). The WHO estimates that exposure to residential radon is responsible for 3-15% of LC cases worldwide and this percentage could be higher in areas of high radon concentration (128). These data coincide with those of a study conducted in Galicia (129).

In an European pooling study, the existence of a linear and significant association between residential radon and LC risk was observed, after finding a 16% increase in the odds of developing LC with every 100 Bq/m3 increase in the concentration of residential radon (130). In addition, there was a synergistic effect between residential radon and smoking habit. An American pooling study conducted simultaneously found similar results (131).

A systematic review observed that, in those areas with the greatest exposure to radon, there was an increased risk of developing LC (132). In fact, one of the included studies, conducted in our area (Galicia, an area with a high concentration of radon), observed a relationship between exposure to residential radon and the existence of LC in never smokers, former smokers and active smokers (133). A previous study had already shown a significant effect of radon exposure from 37 Bq/m3 (134). These studies also revealed the existence of a synergistic effect between tobacco and radon (133-135).

1.3.3.1.2. Family history and genetic exposure.

In the evaluation of patients with LC, it is important to assess any familiar history of LC, a process that can be complex, since members of the same family usually share the same risk factors. However, it does seem that, adjusting for smoking habit, the risk of suffering from LC is greater in the first- and second-degree relatives of a patient who has previously suffered it. Specifically, the risk seems to be higher in people under 59 years of age with a first-degree background. However, the risk is not only given by family history of LC, but also by tumors of

another origin, being the LC more common in families with cases of breast and ovarian cancer (133,135). Despite the fact that certain families can present several LCs in different members, genes of high penetrance have not yet been identified for LC, unlike for other tumors, so we cannot speak familial aggregation of this disease .

To date, there are many genes suspected of playing a role in LC appearance, such as CYP1A1, CYP2D6, CYP2A6, CYP2C9, CYP3A4 and CYP2E1, GSTM1, GSTT1 and GSTP (138-143). GSTM1 and GSTT1 gene deletions increase the risk of developing LC. They are a family of isozymes that play a role in the detoxification of different substrates. Up to 20-50% of Caucasians present deletions in these genes, which cause an enzymatic deficit and, in patients carrying null genotypes for GSTM1 or GSTT1, there is an increased risk of LC compared with carriers of at least one functional allele (144).

1.3.3.2. Risk factors for COPD

Several risk factors have been described to develop COPD, such as age, sex, lung aging, problems during pregnancy, birth or subsequent exposures that may affect lung growth, repeated infections in childhood or adolescence and socioeconomic factors, most of them, being unmodifiable (35).

1.3.3.2.1. Gender and age

Traditionally, it has been stated that age is a risk factor for developing COPD (145). It is not clear whether the effect attributed to age is due to aging itself or to the fact that it involves the accumulation of risk exposures throughout a lifetime. The aging of the airways and parenchyma simulates some of the structural changes associated with COPD (145).

In the previous decades, many studies observed that COPD prevalence and mortality were higher in men than in women. However, more recent data show that COPD prevalence is almost equal in both sexes, probably due to changes in tobacco exposure patterns (146).

1.3.3.2.2. Lung growth and development.

It seems that some processes and exposures during pregnancy, childhood and adolescence can affect lung growth and, therefore, imply an increased risk of developing airflow obstruction (147,148). Several studies have shown an effect of repetition infections during childhood on the likelihood of developing COPD (149).

1.3.3.2.3. Socioeconomic status.

Low socioeconomic status is associated with an increased risk of developing COPD, although the mechanism by which this occurs is not clear (150). It could be due to exposures to certain pollutants, malnutrition and an increased risk of recurrent infections (151).

1.3.3.2.4. Asthma and bronchial hyperreactivity.

Asthma can be a risk factor for chronic airflow obstruction development. In a longitudinal cohort of patients, adults with asthma had a 12 times higher risk of developing COPD than those without asthma, even after adjusting for smoking (152). Another longitudinal study showed that about 20% of subjects with asthma developed irreversible airflow obstruction and decreased diffusion capacity (153).

Bronchial hyperreactivity (without a diagnosis of asthma) has been shown to be a risk factor for developing COPD, also increasing mortality (154-156).

1.3.3.2.5. Infections.

The history of severe infections in childhood has been associated with a reduction in lung function and an increase in respiratory symptoms in adult life (157). The susceptibility to develop infections affects the existence of COPD exacerbations, although its role as a risk factor for developing the disease is not clear. It seems that infection with the human immunodeficiency virus accelerates the onset of emphysema and COPD in smokers, and some authors also associate tuberculosis with an increased risk of developing COPD (158). In the PLATINO study, the history of tuberculosis was associated with a 2 to 4 times higher risk of developing COPD, independently of other risk factors such as smoking (37,159).

1.3.4. COPD as a risk factor for LC development.

Some studies have shown that COPD is a risk factor for LC development, independently of tobacco exposure, with a 4- to 6-fold higher risk of developing LC than smoking patients with normal lung function (15). This risk seems to increase with the progressive fall of FEV_1, independently of the smoking history (68). In addition, COPD conditions a worse LC prognosis because it implies greater morbidity and mortality (160). However, De Torres et al. (161) paradoxically observed that the risk of developing LC was lower as the airflow obstruction progressed.

Squamous carcinoma is the most frequent histological type in patients with COPD or emphysema (161,162), being the most prevalent in patients with COPD with a central LC, as squamous carcinoma is typically located in that area. In cases with incipient or low-grade emphysema, LC will continue to be located in these central regions, while in cases with more extensive emphysema, the most frequent location will be the peripheral one (163).

In histological samples, it seems that adenocarcinoma in patients with COPD tends to show less invasiveness (a greater lepidic component and less cellular proliferation) (164).

There are several hypotheses that could justify COPD being a risk factor for LC development, such as inflammation, oxidative stress, epigenetic alterations or other elements such as hypoxia-inducible factors (which play a relevant role in the development of cancer through the direct control of the expression of epigenetic regulators such as lysine demethylases), VEGF (regulator of angiogenesis), epidermoid growth factor (EGF) and transforming growth factor-beta (TGF-β) (5).

1.3.4.1. Inflammation.

Persistent inflammation of any tissue leads to repair mechanisms that, if perpetuated, can provoke tumor genesis. This happens in the case of the airway, whose maintained inflammation is postulated as one of the physiopathological mechanisms that plays a key role in the amplification of the initial mutagenic response of LC. Possibly, the persistent inflammation in the airway of patients with COPD can induce alterations in the bronchial epithelium that favor carcinogenesis (5). In recent years, the role played by inflammation in COPD has been studied, focusing, for example, in the expression of cytokines such as IL-6, IL-8 and IL-10 that, through the induction of the enzyme cyclooxygenase-2, promote an inflammatory response in lymphocytes. Thus, they inhibit apoptosis, interfere with cell repair and promote angiogenesis, contributing to neoproliferative processes (5,165). Therefore, it seems that the increased risk of developing LC in patients with COPD could be related to the existence of basal inflammation susceptible to the cumulative effects of tobacco, which may persist even years after having quit smoking, and may be a cause of LC in former smokers (5). This aspect will be addressed in this doctoral thesis.

1.3.4.2. Epigenetics and oxidative stress.

An excess in the production of oxygenated and nitrogenous radicals could induce structural and functional cell modifications, as well as epigenetic alterations that would play a role in the development of LC (166,167). Some studies have found high oxidant levels and decreased antioxidants in tissues, negatively affecting cascades of lipid, protein and DNA signaling (168-171).

Some studies postulate that the expression of genes in the initiation and progression of cancer is controlled at the level of translation (172). Others affirm that the protein profiles identified in the bronchoalveolar lavage of patients with COPD, COPD and LC, LC and healthy controls could have a potential use as biomarkers for the early diagnosis of LC (173). In addition, it is also known that LC in patients with COPD differs from that in patients without COPD, since the genes that are expressed and methylated do so differently (174). In addition, a transcriptome has been constructed for NSCLC based on gene expression profiles, using primary tumors and bronchial epithelial cells of the lung (175).

That is why oxidative stress and epigenetic alterations in lung and blood are potential markers of early diagnosis, follow-up and LC prognosis in patients with COPD (5).

1.3.5. LC influence on COPD.

One important issue pending specific studies designed for its assessment, is whether the presence of cancer alters spirometry and, therefore, leads to an overestimation of COPD prevalence. In this study (15), in a subgroup of 127 patients with available respiratory function tests prior to LC diagnosis, they found a small non-significant increase in the prevalence of COPD after the diagnosis of cancer (56 to 61%, $p = 0.45$). This suggests that the overdiagnosis of COPD derived from the existence of the LC itself is modest when compared to the prevalence of a control group of smokers. This was also supported by the fact that pulmonary function (or COPD prevalence) was not significantly affected by the stage of LC. In addition, we must take into account the effect of pulmonary resection as a part of LC treatment on the lung function of the patient, which, in this study, implied a significant increase in the prevalence of COPD, from 44% to 60% ($p = 0.02$) (15).

1.4. EMPHYSEMA AND LC.

1.4.1. Relationship between both entities.

Pulmonary emphysema is a pathological lesion defined by a dilation of the distal airways accompanied by a destruction of their walls. Emphysema may be present in all COPD phenotypes, and even in smokers without airflow obstruction (28). Up to 47-76% of LC patients have pulmonary emphysema (56,176). To note, the prevalence of emphysema in patients with LC is higher than the prevalence of COPD, which could be due to the absence of validated and standardized reference values to clearly define the existence or not of emphysema, so there could be some overdiagnosis of this disease.

Emphysema is the result of apoptosis of pulmonary epithelial cells in response to external noxious stimuli (such as tobacco smoke) and cellular inflammation resulting from the effects of inflammatory molecules on tobacco smoke. Cancer develops when there are clones of cells with mutations resistant to signs of apoptosis originating from tobacco. These cells expand, mutate and eventually become malignant (177).

So far, there are divergent conclusions in the available studies that explore the relationship between LC and emphysema (60,67,178), which can be explained by the emphysema detection method (162) and by the different computed tomography (CT) evaluation methods, observing that emphysema visually detected by an expert radiologist seems superior to automatic detection when establishing it as a risk factor for developing LC, even independently of the presence of airflow obstruction (32,60,67). There are studies that show that the existence of emphysema was associated with an increased risk of LC [RR 3.13 (95%CI 1.32-7.44) and RR 3.56 (95%CI 2.21-5.73)].

Squamous cell carcinoma is the most frequent histological type of LC among patients with emphysema (161,162). However, although in cases with a low degree of emphysema, LC is usually located in central regions, in cases with more extensive emphysema, the most frequent location will be the periphery (163). LC in patients with emphysema seems to be at risk of being more aggressive.

1.4.1.1. Emphysema severity.

There is no validated criteria to quantify the severity of emphysema and, therefore, we do not have data that allow us to establish a clear association between the severity of emphysema and the development of LC. Using automatic quantification, the studies by Kishi et al. (64) and Maldonado et al. (67) did not find any association. However, Wilson et al. (60) and Li et al. (179) found that mild emphysema predicted LC risk better than moderate-severe emphysema. In another study in a US screening cohort, they found a linear association between the severity of emphysema and the risk of death from LC. However, this association was only significant for extensive emphysema (more than half the lung parenchyma) (180). Some studies use the same scale to rate the severity or extent of emphysema, as reflected in the *National Emphysema Treatment Trial* (NETT) guidelines (0: no emphysema, 1: 0-25%, 2: 25-50%; 3 : 50-75%; 4: 75-100%) (176,181).

1.4.1.2. Emphysema types.

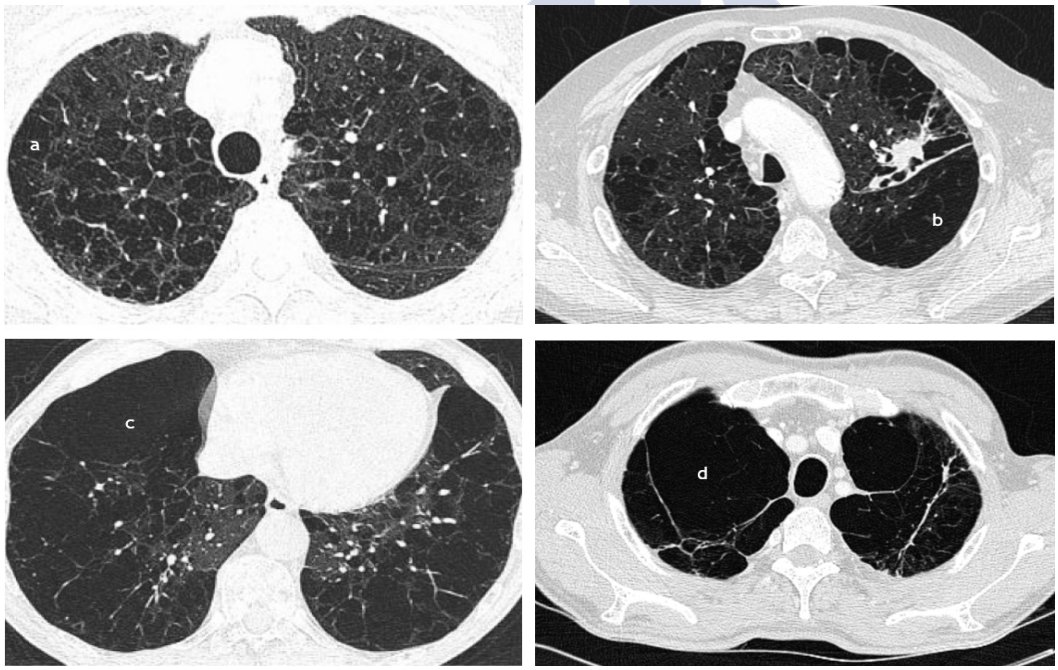

Figure 9. The four images in this figure correspond to four axial slices of a pulmonary CT. The first (a) corresponds to an image of centrilobular emphysema, the second (b) shows an area of paraseptal emphysema, the third (c) shows an image of panacinar emphysema, and the fourth (d) shows the existence of a pulmonary bulla. Figures (a) and (c) have been adapted from Hansel et al. Fleischner Society: Glossary of Terms for Thoracic Imaging. Radiology. 2008; 246 (3):697-722, permitted by Radiology, whereas Figures (b) and (d) belong to two patients in our database which gave specific written informed consent for the anonymized publication of their images..

There are several types of emphysema, although there is no clear evidence about its relationship with the development of LC or other types of disease (162).

Centrilobular emphysema was defined as a dilation of the airway centered in the respiratory bronchiole; paraseptal emphysema as changes in the more distal alveoli adjacent to the pleural surface or to the interlobular septa; panlobular as that distributed throughout the pulmonary lobe; cicatricial as that settled on areas in which there has been some previous type of inflammatory process that has conditioned residual changes in the lung tissue; and bullae are defined as localized areas of emphysema greater than one centimeter in diameter (162,176,182-184).

The centrilobular emphysema is usually associated with a more advanced age, heavier smoking and severity (162,185), while the paraseptal predominantly affects the upper lobes (2,186) and is associated with male sex, older age and interstitial pathology, occurring more frequently in cases with the emphysema-fibrosis combination (162,185). Typically, paraseptal emphysema is not clinically relevant until it is in advanced stages (186) and has not shown any relationship with the development of symptoms in COPD, with the degree of obstruction or with smoking history (162,185).

Panacinar emphysema is common in young patients, is associated with lower BMI and more severe COPD (162,187,188).

1.4.1.3. Emphysema location.

Dividing the lungs into different segments and assigning specific scores for emphysema, a correlation was observed between the severity of regional emphysema and the chances of developing cancer in that specific location (189). Similarly, Hohberger et al. (176) found that, when comparing the location of a malignant nodule with other lung regions of the same patient, the likelihood of having a more severe emphysema in the area where LC was present was significantly higher: OR 1.34 (95%CI: 1.11-1.62). When comparing the location of a benign nodule with other areas of the lung in the same person, the chances of having a more severe emphysema in the areas where the benign nodule was located were 1.11 (95%CI: 0.72-1.72).

1.5. JUSTIFICATION OF THE INVESTIGATION

As it has previously been stated, COPD and LC are high-impact health diseases that share common risk factors, specially smoking. Despite the great advances that have taken place in

the knowledge of both diseases, there are a number of aspects that have been very little analyzed so far, which could have an impact on the healthcare environment. The existence of an association between LC and COPD is an issue under discussion and the available data on the level of underdiagnosis of COPD in patients with LC and its phenotypic and multidimensional characterization is scarce or nonexistent. For this reason, we consider the study of the interrelation of both diseases pertinent and relevant, in order to generate the necessary scientific bases to better understand the interrelation between both pathologies, being able to transfer the results of the research to the clinical practice.

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CHAPTER 2.

JUSTIFICATION AND OBJECTIVES.

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COPD and LC are two diseases with high morbidity and mortality (3,29,42). The high prevalence of patients suffering from both diseases suggests that there may be common etiological mechanisms, not only pathogenic but also genetic (190). Their interrelation is controversial and there are authors who have published studies in an attempt to verify whether COPD is a true risk factor for LC development or if both diseases are the result of common etiological factors, such as inflammation (53). As already explained in the introduction, several studies have shown that COPD is one of the main risk factors for LC development, regardless of sex, age, occupation or tobacco exposure, multiplying the risk from 4 to 6 times, when compared with smokers who maintain an adequate respiratory function (15,178). These probabilities seem to increase as FEV_1 decreases, independently of smoking (68). On the other hand, COPD is one of the complications of LC that implies greater morbidity and mortality (191,192).

Regarding the presence of emphysema, although several studies consider it a risk factor for LC development, it remains a controversial issue since other works do not report the same finding (193).

So far, it has not been studied whether patients with COPD and LC have any differential characteristics compared to patients with COPD without LC, in terms of their phenotypic characterization, multidimensional aspects or comorbidities, issues that are key in the new vision of LC, with implications in the choice of targeted therapies and in the prognostic stratification. It is also unknown how the stage of the neoplastic disease impacts on COPD, a fundamental aspect in the clinical evolution of this disease. On the other hand, although there are several types of emphysema, there is no clear evidence about its relationship with LC development.

Certain inflammatory markers have been associated in COPD with increased mortality and exacerbations, as well as with the risk of progression and worse prognosis in LC (194-203). The finding of common biomarkers that can establish prognostic and therapeutic response categories would be an important tool in decision making and could even mean the identification of COPD patients at risk of developing LC.

For this reason and based on the potential association between COPD and LC, this thesis was designed to carry out research in order to better understand the interaction between both

diseases, as well as establishing whether there is any relationship between the type of pulmonary emphysema and the development of LC or some biomarker that may suggest a greater risk of belonging to the group of patients with COPD and LC. Having clinical, functional, imaging or biochemical predictors to detect patients with COPD who also have LC, would help to avoid unnecessary invasive procedures (or even to detect early LC) in these cases.

The general objective of the project is to estimate COPD prevalence and its degree of underdiagnosis in patients with LC, as well as to evaluate the clinical profile of patients with COPD and LC, comparing it with another control group of patients with COPD but without LC, analyzing its phenotypic and multidimensional characterization and looking for a potential utility in the early detection of LC in patients with COPD or even with therapeutic or prognostic implications. The following specific objectives were established:

1. To estimate COPD prevalence among patients with LC diagnosis, as well as the degree of COPD underdiagnosis in this group (previously undiagnosed patients in whom COPD was detected in the spirometry performed at the time of LC diagnosis).
2. To analyze, within patients with LC, the differential clinical characteristics of patients with concomitant COPD.
3. To evaluate the clinical profile of patients with COPD and LC, comparing it with another control group of patients with COPD without LC, analyzing their phenotypic and multidimensional characterization.
4. To assess if there is a relationship between a specific type of emphysema and the existence of LC in patients with COPD.
5. To compare a series of inflammatory markers between patients with COPD and LC and patients with COPD without LC to be able to propose a hypothesis to establish a possible early detection strategy for LC in COPD patients.

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CHAPTER 3.

SUBJECTS AND METHODS.

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Initially, and considering the importance of a potential relationship between COPD, emphysema and the development of LC, a systematic review of the literature was carried out to analyze the available scientific evidence on this association, subsequently developing the present research project.

In order to carry out this thesis, four works were therefore designed:

1. A systematic review (already explained in the previous paragraph).
2. A prospective cohort study with the aim of describing the frequency and phenotypic characteristics of patients diagnosed synchronously with COPD and LC.
3. An observational case-control study, being the cases patients with COPD and LC and the controls, patients with COPD without LC. In this group of patients, the phenotypic characterization and the impact of COPD were analyzed by means of clinical assessments, necessary questionnaires and the evaluation of pulmonary CT.
4. A prospective case-control study in which blood levels of the following analytical parameters were compared in three groups of patients (COPD without LC, LC without COPD and COPD and LC): interleukins 6 and 8 (IL-6 and IL-8), fibrinogen, tumor necrosis factor (TNF-α), C-reactive protein (CRP), leukocytes, lymphocytes, neutrophils, neutrophil-lymphocyte ratio (NLR), platelets, mean platelet volume (MPV), platelet-lymphocyte ratio (PLR), A1AT, immunoglobulin E (IgE), cholesterol and bilirubin.

This project has the favorable evaluation of the *Clinical Research Ethics Committee of Galicia* (file 2013/439), whose report is attached in the Annex. All patients signed a written informed consent. All data were included in a confidential and anonymized database.

3.1. Design and Setting.

To carry out the systematic review, we included cohort studies, case and control studies, systematic reviews or meta-analyzes, which included at least 500 individuals. According to the diagnostic criteria for COPD, we included patients over 35 years of age with an accumulated tobacco consumption of more than 10 pack-years and an irreversible obstructive spirometry. Regarding emphysema diagnosis, we included studies with a quantitative or qualitative evaluation by CT. Only studies with histological confirmation of the diagnosis of LC were included.

Subsequently, an observational study of prospective cohorts and two case-control studies of patients with LC, COPD and COPD with LC were designed. In these groups of patients, the phenotypic characterization, the impact of COPD through the clinical assessments and necessary questionnaires and also the existence of emphysema were analyzed comparatively. Blood levels of a panel of 16 biomarkers, which are detailed below, were also compared.

The cohort study including patients with LC with or without COPD is a multicenter study that includes patients from two hospitals: the Complexo Hospitalario Universitario de Vigo and the Complexo Hospitalario Universitario de Ourense. The second and third studies include patients from the Complexo Hospitalario Universitario de Vigo. The Complexo Hospitalario Universitario de Vigo is a third-level center with a health area of 450,000 inhabitants, while the Complexo Universitario Hospitalario de Ourense is a second-level center with an area of 255,000 inhabitants. The Pneumology Service of the Complexo Hospitalario Universitario de Vigo performs practically all available pulmonary and pleural procedures and techniques, with several accredited units of maximum complexity, and includes a Lung Cancer Rapid Diagnosis Unit (LCRDU) as part of a multidisciplinary approach initiated by an electronic system where radiologists alert pulmonologists when there is a radiological suspicion of LC. This unit evaluates about 95% of all patients with LC in the area.

3.2. INCLUSION CRITERIA.

In all three studies, adult patients of both sexes were included. For COPD diagnosis patients older than 35 years were included.

The first study included patients diagnosed with LC from January 2014 to August 2016.

In the second study, the cases were patients with COPD and LC obtained from the previous study and controls, patients diagnosed with COPD in the 6 months prior to the study start, without LC and coming from the general pneumology consultations. Both cases and controls had to have a thoracic CT at diagnosis for emphysema evaluation. Patients were included from January 2014 to September 2016.

In the third study, cases were patients with COPD and LC diagnosed in the LCRDU, while controls (patients with COPD and without evidence of LC) were recruited in a general pulmonary consultation that was carried out on the same days as the LCRDU, including patients with recently diagnosed COPD (less than 6 months). A second group of controls with LC with

normal lung function was included to make a descriptive comparison of the levels of inflammatory markers among the three groups. Patients were included from September 2014 to May 2018.

3.3. Exclusion Criteria.

Underage patients, patients who expressed their desire not to participate in the study, patients with contraindications or inability to perform a spirometry and finally, patients with a known disease with airflow obstruction different from COPD. All patients who did not want or did not need a chest CT scan were excluded from the second study, in accordance with the recommendations of the COPD guidelines (29,42). Those patients who did not wish to perform a peripheral blood test, those with simultaneous active infections or inflammatory processes and those with a synchronous neoplasia other than LC were excluded from the third study.

3.4. Sample Size Calculation.

For the calculation of the sample size, a COPD prevalence among patients with LC of a 40% was taken (192). Applying an accuracy of 5% and a confidence level of 95%, a sample size of 369 patients who met the inclusion criteria was obtained. Adding 5% for possible losses, we obtained a final sample size of 388 patients, so finally, the estimated sample size was 400 patients.

3.5. Information Retrieval.

In all the patients an evaluation of different characteristics was carried out:

1. Epidemiological and clinical: age, sex, body mass index (BMI), smoking habit, occupational risk exposure or history of cancer, through the development of the clinical history. In addition, the degree of dyspnea was evaluated through the scale of the Medical Research Council (MRC).

2. Basal clinical situation: patient's general condition (ECOG scale) and degree of comorbidity measured by the Charlson index.

3. Respiratory function tests: All patients with LC underwent spirometry with a bronchodilator test according to established recommendations. The functional parameters that were collected were FEV_1, FVC and FEV_1/FVC. A determination of the DLCO and the KCO (carbon monoxide transfer coefficient) was also carried out.

4. LC characteristics: histological type (SCLC and NSCLC, adenocarcinoma, squamous cell carcinoma or large cell carcinoma) and TNM stage according to the current edition at the time of the study (27,204).

5. COPD characteristics: severity according to the GesEPOC guidelines (*Spanish COPD guidelines*) and GOLD (*Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease*) valid at the time of the study (29,42), in addition to recording the number of moderate exacerbations and hospitalizations for COPD in the last year and an assessment of the impact of the disease on quality of life through the COPD Assessment Test (CAT).

6. Emphysema characteristics: the presence of emphysema in thoracic CT was evaluated within the group of patients with COPD (with or without LC). The CT studies were carried out in two equipments: Lightspeed VCT of 64 rows of detectors (GE Medical Systems, Milwakee, Wisconsin) and Somatom Emotion of 16 rows of detectors (Siemens Medical Solutions, Enlargen, Germany). A qualitative and quantitative analysis of the type of emphysema was carried out, as well as the existence of different types of it, its affectation by lobes and its severity.

7. Relationship between COPD and LC: the COPD-LUCSS-DLCO scale described by De-Torres (80) was calculated.

8. Analytical: Peripheral venous blood samples of all patients were extracted. The serum concentrations of IL-6, IL-8 and TNF-α were determined by validated immunoassays (IMMULITE ONE, Siemens, Germany), complete blood counts were performed using ADVIA 2120 (Siemens, Germany), serum CRP, cholesterol and bilirubin were measured using ADVIA 2400 (Siemens, Germany); A1AT was analyzed by nephelometric assay (IMMAGE, Beckman Coulter, U.S.A.). IgE levels were measured by fluorometric immunoassay (PHADIA 250, Thermo Scientific, USA) and fibrinogen was calculated in the ACL TOP 700 instrument (Werfen Company, Spain). The detection limits (DL) for IL-6, IL-8 and TNF-α were 2 pg/ml, 5 pg/ml and 4 pg/ml. To avoid a downward bias of the data obtained, a nominal level of half the DL value in the analysis was used in individuals with values lower than the LD (205).

3.6. STATISTICAL ANALYSIS.

A descriptive analysis of all the included variables was carried out. Subsequently, bivariate analyzes were performed to evaluate the differences between groups. Student's t was used for quantitative variables and the $\chi 2$ test for qualitative variables. The significance limit was $p < 0.05$. The significant variables in the bivariate analysis were included in a logistic regression model, expressing the data as OR with 95% confidence intervals. The Kaplan-Meier method was used to perform survival estimates. In the third study, two multivariate logistic regression models were performed, the first adjusting by age and sex and the second including the significant variables in the first. To do this, the quantitative variables were stratified into tertiles for inclusion in the logistic regression models. This led to the design of a risk variable for each patient based on the results of the logistic regression. Subsequently, a ROC curve was developed to evaluate the sensitivity, specificity and predictive values of the risk variable, taking into account a prevalence of LC in patients with COPD of 25% (15). The analysis was performed with the SPSS 21.0 program (IBM Corporation, Armonk, New York).

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CHAPTER 4.

RESULTS

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This section presents the results in 4 chapters, each of them reflecting the different studies resulting from this thesis:

1. **CHAPTER 5. "COPD, emphysema and the onset of lung cancer. A systematic review".**

   The results of this study show that COPD and emphysema appear to increase the risk of developing LC, this risk being higher for patients with greater tobacco consumption.

2. **CHAPTER 6. "COPD in lung cancer patients: prevalence, underdiagnosis and clinical characterization".**

   The results of this study show that COPD is a prevalent and highly underdiagnosed disease among LC patients. Cases with COPD and LC have a higher prevalence of squamous cell carcinoma, more comorbidities and lower KCO.

3. **CHAPTER 7. "Influence of the type of emphysema in the relationship between COPD and lung cancer".**

   The results of this study show that paraseptal emphysema is more frequent in patients with COPD and LC, especially in those cases with the adenocarcinoma subtype

4. **CHAPTER 8. "Predictive value of a series of inflammatory markers in COPD for lung cancer diagnosis".**

   The results of this study show that patients with COPD and LC have higher levels of neutrophils and A1AT and lower concentrations of cholesterol, having developed with their combination a scale that predicts the risk of belonging to the group of patients with COPD and LC.

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CHAPTER 5. RESULTS. COPD, EMPHYSEMA AND THE ONSET OF LC. A SYSTEMATIC REVIEW

CHAPTER 6. RESULTS.

COPD IN LC PATIENTS: PREVALENCE, UNDERDIAGNOSIS AND CLINICAL CHARACTERIZATION.

CHAPTER 7. RESULTS. INFLUENCE OF THE TYPE OF EMPHYSEMA IN THE RELATIONSHIP BETWEEN COPD AND LC.

CHAPTER 8. RESULTS

PREDICTIVE VALUE OF A SERIES OF INFLAMMATORY MARKERS IN COPD FOR LC DIAGNOSIS.

Predictive value of a series of inflammatory markers in COPD for lung cancer diagnosis.

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Abstract

Introduction: There is a relationship between Chronic Obstructive Pulmonary Disease (COPD) and the development of lung cancer (LC). The aim of this study is to analyse several blood markers and compare their concentrations in patients with only COPD and LC+COPD.

Methods: Case-control study with cases presenting combined LC and COPD and two control groups (patients presenting only COPD and patients presenting only LC). We also included LC patients with descriptive purposes. In both groups, peripheral blood analyses of TNF-α, IL-6, IL-8, total leukocyte, lymphocyte and neutrophil counts, neutrophil-to-lymphocyte ratio, total platelet count, mean platelet volume, platelet-to-lymphocyte ratio, alpha 1-antitripsin (A1AT), IgE, C-reactive protein, fibrinogen, cholesterol and bilirubin were

performed. We developed univariate and multivariate analyses of these markers, as well as a risk score variable, and we evaluated its performance through ROC curves.

Results: We included 280 patients, 109 cases (LC+COPD), 83 controls (COPD) and 88 LC without COPD. No differences were observed in the distribution by sex, age, BMI, smoking, occupational exposure, lung function, GOLD stage or comorbidity. Patients with LC+COPD had significantly higher levels of neutrophils [OR 1.00 (95%CI 1.00-1.00), p=0.03] and A1AT [OR 1.02 (95%CI 1.01-1.03), p=0.003] and lower cholesterol levels [OR 0.98 (95%CI 0.97-0.99), p=0.009] than COPD controls. We developed a risk score variable combining neutrophils, A1AT and cholesterol, achieving a sensitivity of 80%, a negative predictive value of 90.7% and an area under the curve of 0.78 (95%CI 0.71-0.86).

Conclusions: COPD patients who also have LC have higher levels of neutrophils and A1AT and lower of cholesterol. These parameters could be potentially predicting biomarkers of LC in COPD patients.

Keywords

Lung cancer

COPD

Neutrophils

A1AT

Cholesterol

Introduction

Lung cancer (LC) is the leading cause of cancer death worldwide, with a 5-year survival of approximately 15%. Chronic Obstructive Pulmonary Disease (COPD) is the fourth cause of death worldwide, with a current prevalence around 10%[1-3]. LC mortality is explained by the fact that most diagnoses are made in advanced stages, being able to identify tumors in localized stages only in 16-22% of cases, although new diagnostic techniques and the implementation of rapid diagnostic units are increasing the proportion of patients diagnosed with localized LC[2-4]. In these cases, survival can reach up to 55.6% at 5 years[5].

Some studies have demonstrated that COPD is a risk factor for LC development, independently of tobacco exposure. In addition, COPD and LC share some common features. Smoking is the main cause of both diseases, COPD affecting 15-20% of smokers, while 80% of LC patients are smokers or ex-smokers. Besides tobacco use, COPD and LC share some genetic backgrounds, environmental exposures, and common underlying inflammatory processes[6,7].

Airway chronic inflammation is one of the pathophysiological mechanisms that plays a key role in the amplification of the initial mutagenic response of LC. It is possible that persistent airway inflammation in COPD patients induces alterations in the bronchial epithelium which favor carcinogenesis[8]. In patients with COPD and in smokers, the expression of certain cytokines is increased, such as IL-6 and IL-8, which, in turn, through the induction of the enzyme cyclooxygenase-2, promote an inflammatory response in lymphocytes. They can also inhibit apoptosis, interfere with cellular repair mechanisms and promote angiogenesis, contributing to neoproliferative processes[8]. Other cytokines and growth factors such as tumor necrosis factor (TNF)-α have also been shown to participate in the development, tumor growth and metastasis of LC in patients with underlying respiratory conditions[9]. In fact, various blood markers of inflammation have been evaluated separately in patients either with COPD or with LC and other malignant tumors (Table 1). These markers include C-reactive protein (CRP), platelet, neutrophil, and lymphocyte numbers but especially include neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), mean platelet volume (MPV), alpha-1-antitripsin (A1AT), fibrinogen, cholesterol or bilirubin[10-14]. Therefore, the increased risk of developing LC in patients with COPD could be related to the existence of a previous inflammation, making them more susceptible to the carcinogenic components of tobacco. This inflammation persists

even years after having stopped smoking, which may be a cause of LC in ex-smokers[8]. To our knowledge, there are no studies assessing a complete series of inflammatory blood markers in patients with COPD comparing them with LC+COPD patients. To have some predictive markers in COPD patients showing a higher possibility of LC would mean an early diagnosis and therefore improving their clinical results. We have selected 16 biomarkers in order to test the importance of persistent airway inflammation in the development of LC in COPD patients, as these markers have already shown to be high in COPD and related to disease progression, prognosis and response to treatment in LC.

The aim of this study is: 1) to assess a panel of different markers (IL-6, IL-8, TNF-α, CRP, PCR, IgE, platelet, neutrophil, and lymphocyte numbers, NLR, PLR, MPV, A1AT, fibrinogen, cholesterol and bilirubin) in three groups of patients (COPD, patients with COPD and LC [LC+COPD] and LC without COPD), focusing on the comparison between COPD and LC+COPD patients and, 2) to select those markers associated with LC+COPD and to create a score to predict the risk of presenting LC based on selected clinical parameters.

Table 1. Markers selected for the development of a diagnostic panel for LC+COPD

Marker	Role in COPD	Role in LC
TNF-α	Mortality was 6-times higher in patients with high WBC, CRP, IL-6, IL-8, TNF- α and fibrinogen[10].	TNF- α levels are increased in patients with LC+COPD when compared to COPD and healthy patients[38].
IL-6	Its increase predicts mortality from COPD[25].	High concentrations of IL- 6 increases LC risk and worsens LC prognosis[30].
IL-8	Mortality was 6-times higher in patients with high WBC, CRP, IL-6, IL-8, TNF- α and fibrinogen[10].	It shows good sensitivity to diagnose LC in healthy and COPD patients. Higher concentrations increase LC risk[39].
Leukocytes	Mortality was 6-times higher in patients with high WBC, CRP, IL-6, IL-8, TNF- α and fibrinogen. Higher levels are associated with exacerbation risk[10].	They are increased in patients with LC+COPD when compared to COPD and healthy patients[38].
Lymphocytes	Lymphocyte count is significantly associated with exacerbation risk[27].	Total lymphocyte count is associated with disease progression during LC treatment[11,33].
Neutrophils	Neutrophils predispose towards increased inflammation and reduced bacterial clearance in COPD patients, especially during exacerbations[40].	Neutrophils are increased in patients with LC+COPD when compared to COPD and healthy patients. It is an independent indicator of poor prognosis[11,33,38].
NLR	NLR is higher in hospitalized non-eosinophilic COPD patients[41].	NLR is higher in LC patients when compared to healthy controls. It has been proposed as an independent prognostic factor for survival[11,33].
Platelets	Platelets are higher in COPD exacerbations. They have a role at predicting bacterial infections[28].	Platelets are higher in LC patients when compared to healthy controls. They are associated with poor prognosis in local and advanced LC[11].
MPV	MPV is higher in COPD exacerbations[42].	MPV is lower in LC patients when compared to healthy controls[11].
PLR	PLR is higher in COPD exacerbations. It has a role at predicting bacterial infections[28].	PLR is higher in LC patients when compared to healthy controls and it was found to be an adverse prognostic factor in NSCLC[11].
Fibrinogen	An increase in fibrinogen levels of 1 g/l is associated with a 3.5-fold increase in COPD mortality[10].	An elevated serum fibrinogen level was associated with poor prognosis in NSCLC[12].
A1AT	The congenital deficiency of alpha-1-antitrypsin is responsible for about 1% of COPD cases and 2-4% of emphysema cases[34].	Higher A1AT levels promote lung adenocarcinoma metastasis[13].
IgE	There is a high prevalence of elevated IgE levels in COPD patients[29].	Higher levels of IgE are associated with LC risk in healthy subjects[31].
CRP	Mortality was 6-times higher in patients with high WBC, CRP, IL-6, IL-8, TNF-α and fibrinogen. It increases risk of hospitalization and mortality[10].	An increase in 1 SD of the CRP levels increases the risk of dying by CP 2.32 times. Higher levels impact on survival in operable LC[32].
Cholesterol	Hyperlipidemia increases COPD mortality[43].	Cholesterol levels are lower in LC patients when compared to healthy controls[11].
Bilirubin	A reduction of 1mg/dl in bilirubin levels is associated with an increase of 86% in mortality associated with COPD[26].	Direct bilirubin levels are correlated with tumor progression, response to chemotherapy, and survival[14].

TNF-: tumor necrosis factor; IL: interleukine; NLR: neutrophil to lymphocyte ratio; MPV: mean platelet volume; PLR: platelet to lymphocyte ratio; A1AT: alpha 1-antitripsin; IgE: E-immunoglobulin; CRP: C-reactive protein; COPD: chronic obstructive pulmonary disease; LC: lung cancer; WBC: white blood count; NSCLC: non-small cell lung cancer; SD: standard deviation.

Material and methods

Study design and case and control selection

This is a case-control study in which patients with COPD, with LC+COPD and with LC only were included from September 2014 to May 2018 from the Vigo University Hospital. This hospital attends a 450,000-inhabitant area, and the pulmonary department applies practically all pulmonary techniques and procedures. Cases were COPD patients with synchronic LC (LC+COPD) diagnosed in the Lung Cancer Rapid Diagnosis Unit (LCRDU), while controls (patients with COPD and no evidence of LC) were captured in a general pulmonary consultation that was carried out on the same days as the LCRDU, including patients with recently-diagnosed COPD (less than 6 months). We included a second group of controls with LC with normal lung function to make a descriptive comparison of inflammatory marker's levels between the three groups. The LCRDU permits a diagnostic and staging process of LC and other thoracic neoplasms. This unit assesses around 95% of all LC patients in our area. Patients with other active tumors different from LC were not included in this study. We also excluded patients with any other active infectious or inflammatory diseases to avoid false positives when assessing blood markers.

The diagnosis of LC was made after suggestive radiological findings with pathologic confirmation[15]. COPD was defined following the *Global Initiative for Obstructive Lung Disease* (GOLD) recommendations as the presence of persistent respiratory symptoms and a forced expiratory volume in the first second (FEV_1)/ forced vital capacity (FVC) ratio <0.70 after a bronchodilator test[16]. We excluded patients unwilling to participate or to donate blood samples, those with contraindications or incapable of performing spirometric tests correctly, and patients with any other pulmonary obstructive disease other than COPD.

We assessed a panel of different blood markers in the three groups of patients: IL-6, IL-8, TNF-α, CRP, IgE, platelet, neutrophil, and lymphocyte numbers, NLR, PLR, MPV, A1AT, fibrinogen, cholesterol and bilirubin, and whether patients were receiving growth factors or statins. All biomarkers were tested in a stable phase, in outpatients, without any concomitant infection or inflammatory process, and without any synchronous tumor.

The study was approved by the Ethics Committee for Clinical Research of Galicia (expedient 2013/439). Informed consent was obtained from all individual participants included

in the study. Variables were included in an anonymized database to maintain the principles of confidentiality and data protection.

Information retrieval

Collected data included basic demographics: age, gender, tobacco history, functional variables (comorbidity assessed by the Charlson Comorbidity Index[17], FEV_1, DLCO and body mass index (BMI). The histological type of LC was also included by reviewing the pathology report, as well as the stage at diagnosis according to the TNM eight edition's descriptors[15] after complete staging processes. Other data necessary for COPD characterization were included, such as the GOLD and *Spanish Guideline for COPD* (GesEPOC) classifications valid at the study onset[16,18], COPD assessment test (CAT)[19] and BODEx index[20].

Smokers were defined as participants who had smoked 100 or more cigarettes in their lifetime. Current smokers were those who smoked more than one cigarette in the month prior to enrollment or quit within one year of enrollment. The remaining smokers were classified as ex-smokers. Never smokers were defined as having smoked less than 100 cigarettes in their lifetime[21].

Spirometry was performed at the time of inclusion in the study by a technician specialized in respiratory functional tests. It was carried out with a Masterlab pneumatic-type spirometer (Jaeger AG, Wuezburg, Germany), using acceptability and reproducibility criteria from SEPAR and ERS[22] guidelines, with Quanjer Gli reference values[23]. A bronchodilator test was performed in all cases, by administrating 400 µg of salbutamol in 4 puffs (100 µg per puff) at 30 s intervals.

Emphysema was determined through computed tomography (CT) assessment by experimented radiologists. The CT studies were performed in two devices: Lightspeed VCT of 64 rows of detectors (GE Medical Systems, Milwaukee, Wisconsin) and Somatom Emotion of 16 rows of detectors (Siemens Medical Solutions, Enlargen, Germany).

Peripheral venous blood was collected from all patients into Vacutainer tubes in the morning. Serum was obtained by centrifugation of whole blood at 3,000 g for 10 minutes. Plasma (CITRATE as anticoagulant) was obtained by centrifugation at 3,500 g for 15 minutes at a temperature of 4ºC. Serum samples used to measure IL-6, IL-8 and TNF-α levels were stored at -80ºC until they were analyzed. IL-6, IL-8 and TNF-α serum concentrations were

determined by validated immunoassays (IMMULITE ONE, Siemens, Germany), full blood counts were carried out using ADVIA 2120 (Siemens, Germany); serum CRP, cholesterol and bilirubin were measured using ADVIA 2400 (Siemens, Germany); A1AT was analyzed by nephelometric assay (IMMAGE, Beckman Coulter, USA); IgE levels were measured by fluorometric immunoassay (PHADIA 250, Thermo Scientific, USA) and fibrinogen was calculated in ACL TOP 700 instrument (Werfen Company, Spain) Limits of detection (LOD) for IL-6, IL-8 and TNF-α were 2 pg/ml, 5 pg/ml and 4 pg/ml. Biomarker concentrations were below the LOD in some individuals. To avoid a downward bias of the population data, a nominal level of half of the LOD value was used in the analysis in individuals with values below the LOD[24].

Statistical analysis

We first carried out a descriptive analysis of levels of all markers in the three groups of patients through the use of boxplots. Then we developed a univariate analysis to evaluate differences between cases (patients with LC+COPD) and controls (COPD) for all assessed variables. The t-student test was used for quantitative variables and Chi^2 test was used to compare percentages for qualitative variables. Our limit of significance was $p<0.05$. We included variables with a $p<0.10$ in the multivariate models (performed through a forward conditional method), developing interaction analyses for all of them. For the final significant variables, we performed two multivariate logistic regression models, the first adjusting for age and sex and the second also including the remaining variables. To do so, the significant quantitative variables were stratified into terciles for inclusion in the logistic regression models. Application of this multivariate analyses led to the design of a risk score variable for each given patient based on the results of the multivariate logistic regression. Points for a given patient were obtained by summing all the points for each predictor variable, adjusted for sex and age. Then we developed a ROC curve and assessed sensitivity, specificity and predictive values for the risk score variable, considering a prevalence of LC in patients with COPD of 25%[7]. The analysis was performed with SPSS 21.0 (IBM Corporation, Armonk, New York).

Results

We included 280 patients: 109 cases (LC+COPD), 83 controls (COPD) and 88 LC patients. A descriptive and univariate analysis comparing baseline characteristics and marker levels of cases and controls is included in Table 2.

Table 2. Univariate analysis comparing characteristics of cases and controls.

	Cases (LC+COPD)	Controls (COPD)	p
Baseline characteristics			
Gender (male), n (%)	95 (87.1)	65 (78.3)	0.07
Age, mean (SD)	67 (10.3)	64.6 (9.4)	0.10
BMI, mean (SD)	26.6 (4.2)	27.3 (4.5)	0.29
Laboral exposure, n (%)	43 (39.4)	25 (30.1)	0.31
Tobacco history, n (%)	109 (100)	82 (98.8)	0.43
Active smokers, n (%)	62 (56.9)	45 (54.2)	0.39
Pack-years, mean (SD)	49.5 (23.8)	47.5 (25)	0.61
Emphysema, n (%)	68 (62.4)	38 (45.8)	0.32
GOLD I-II, n (%)	87 (79.8)	66 (79.5)	0.55
GesEPOC A (%)	105 (96.3)	80 (96.4)	0.65
Bodex, mean (SD)	1 (1.5)	0.8 (1.2)	0.30
CAT, mean (SD)	10.6 (6.2)	9.7 (7.6)	0.69
FEV_1 (%), mean (SD)	69.1 (21.1)	71 (20.2)	0.55
DLCO (%), mean (SD)	68.1 (21)	70.4 (22.6)	0.58
Charlson index, mean (SD)	1.0 (1.5)	0.7 (1)	0.11
Statin consumption, n (%)	40 (36.7)	31 (37.3)	0.52
Inflammatory markers			
TNF-α (pg/ml), mean (SD)	14.7 (46.4)	9.3 (7.4)	0.25
IL-6 (pg/ml), mean (SD)	10.7 (16.6)	6.2 (12.1)	0.05
IL-8 (pg/ml), mean (SD)	29.6 (44.1)	19.2 (28.8)	0.07
Leukocytes (per µl), mean (SD)	10,004,4 (11,096.3)	7,706.1 (2,334)	0.04
Lymphocytes (per µL), mean (SD)	2,334 (1,987.4)	2,398.5 (965.7)	0.77
Neutrophils (per µl), mean (SD)	5,920 (2,469.1)	4,464.2 (2,136.7)	<0.001
NLR, mean (SD)	3.1 (1.8)	2.1 (1.5)	<0.001
Platelets (per µl), mean (SD)	295,114,1 (124,102.4)	243,402.4 (72,978.9)	0.001
MPV (fl), mean (SD)	8.4 (1.2)	8.9 (1)	0.003
PLR, mean (SD)	154 (86.6)	118.5 (72.1)	0.003
Fibrinogen (mg/dl), mean (SD)	461 (198.7)	392.5 (166.5)	0.07
A1AT (mg/dl), mean (SD)	174 (49.9)	136.8 (29.1)	<0.001
IgE (kU/l), mean (SD)	155,7 (109.7)	177.8 (569.3)	0.78
CRP (mg/l), mean (SD)	22 (31.7)	6.1 (8.8)	<0.001
Cholesterol (mg/dl), mean (SD)	178.3 (37.1)	201.8 (37.1)	<0.001
Bilirrubin (mg/dl), mean (SD)	0.6 (0.3)	0.6 (0.2)	0.50

BMI: Body mass index; GOLD: Global Initiative for Obstructive Lung Disease; GesEPOC A: non exacerbators, according to the Spanish Guidelines of COPD; CAT: COPD Assessment Test; FEV1: forced expiratory volume in the first second; DLCO: carbon monoxide diffusion capacity; IL: interleukin; NLR: neutrophil/lymphocyte ratio; MPV: mean platelet volume; PLR: platelet/lymphocyte ratio; A1AT: alpha 1-antitripsin; IgE: E immunoglobulin, CRP: C reactive protein.

As shown in the table, baseline characteristics of both groups were very homogeneous, with no relevant differences between groups, also in terms of baseline treatments. There were

no patients undertaking any growth factor. One case and two controls had A1AT<90 mg/dl. Five patients had cachexia, four were cases (one in the group with high cholesterol levels and three with medium cholesterol levels) and one was a control. Baseline characteristics of LC patients without COPD are included in Table 3.

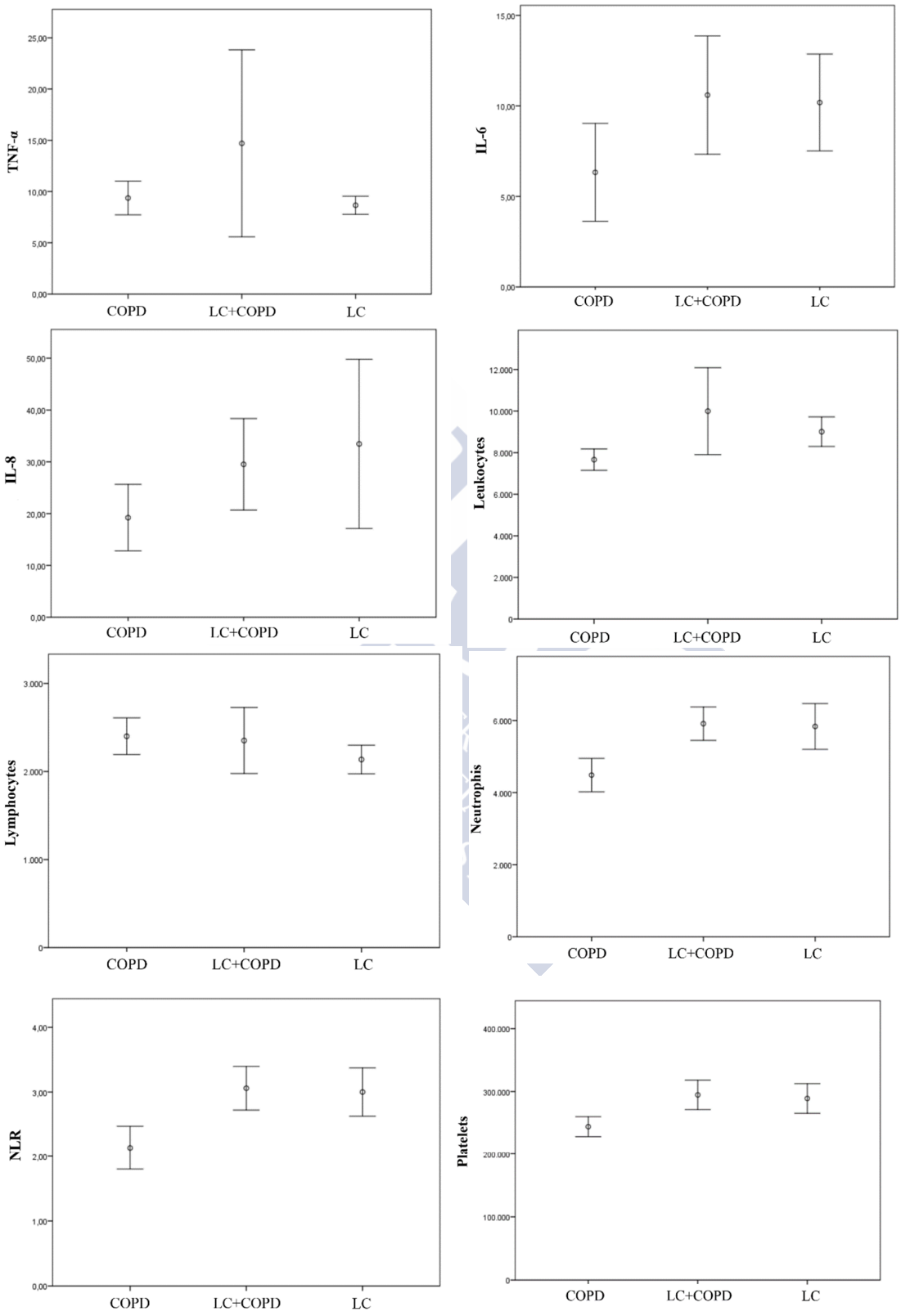
Table 3. Characteristics of patients with LC only.

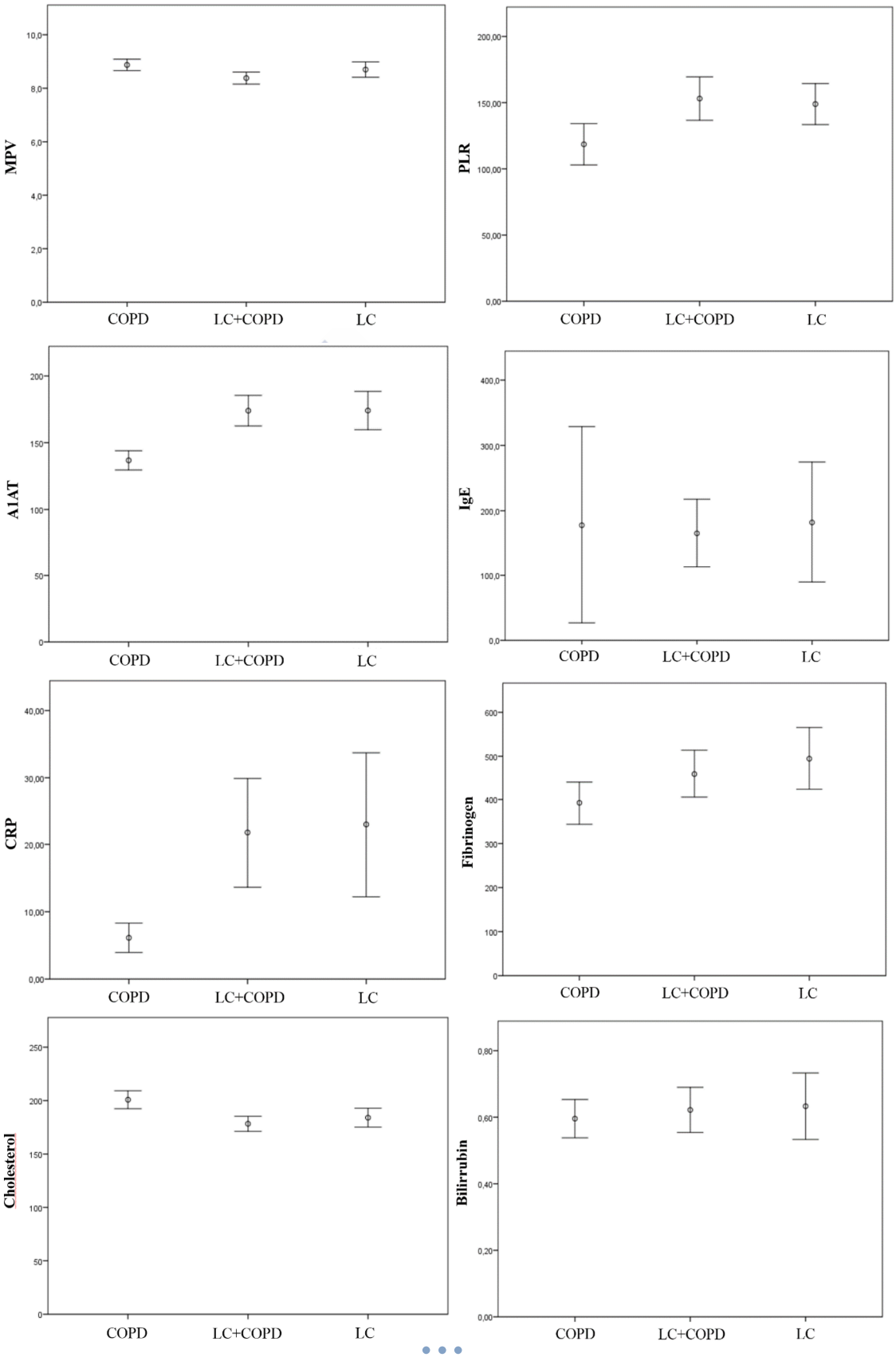
	LC patients without COPD
Gender (male), n (%)	63 (71.6)
Age, mean (SD)	65.7 (10.9)
BMI, mean (SD)	29.3 (5.3)
Laboral exposure, n (%)	28 (33.7)
Tobacco history, n (%)	73 (83)
Active smokers, n (%)	39 (44.3)
Pack-years, mean (SD)	40.3 (23.11)
SCLC, n (%)	4 (4.9)
Adenocarcinoma n(%)	42 (54.5)
Squamous, n (%)	20 (25)
Advanced stage at diagnosis, n (%)	41 (48.2)
FEV_1 (%), mean (SD)	87 (20.8)
DLCO (%), mean (SD)	82.2 (20.3)
Charlson index, mean (SD)	2 (2.2)

BMI: Body mass index; SCLC: small cell lung cancer; FEV1: forced expiratory volume in the first second; DLCO: carbon monoxide diffusion coefficient.

The most frequent histological type was adenocarcinoma, in 84 cases (44.9%), followed by squamous (26.7%), undifferentiated (18.2%), small-cell LC (SCLC) (7%) and carcinoid (3.2%). Regarding tumour characteristics, when comparing LC+COPD with LC patients, we found that patients with LC without COPD had more adenocarcinomas (54.5% vs 38.4%; p=0.02), whereas patients with LC+COPD had more SCLC (17.8% vs 4.9%; p=0.006). There were no differences in stage at diagnosis. Figure 1 shows descriptive boxplots for all inflammatory markers in the three groups of patients.

Figure 1. Descriptive comparison between levels of biomarkers in the three groups of patients




MPV
10,0
8,0
6,0
4,0
2,0
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COPD
LC+COPD
LC
PLR
200,00
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50,00
0,00
COPD
LC+COPD
LC
A1AT
200
150
100
50
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COPD
LC+COPD
LC
IgE
400,0
300,0
200,0
100,0
0,0
COPD
LC+COPD
LC
CRP
40,00
30,00
20,00
10,00
0,00
COPD
LC+COPD
LC
Fibrinogen
600
500
400
300
200
100
0
COPD
LC+COPD
LC
Cholesterol
250
200
150
100
50
0
COPD
LC+COPD
LC
Bilirrubin
0,80
0,60
0,40
0,20
0,00
COPD
LC+COPD
LC

We developed a multivariate logistic regression model comparing cases and controls (Table 4).

Table 4. Multivariate analysis comparing characteristics of cases and controls with variables stratified by terciles.

Variable	Cases, n (%)	Controls, n (%)	OR (95%CI) [a]	p	OR (95%CI) [b]	p
A1AT (mg/dl)						
Low: <138	27 (24.7)	41 (49.4)	1 (-)		1 (-)	
Medium: ≥138 and <167	32 (29.3)	32 (38.5)	1.49 (0.66-3.39)	0.34	0.96 (0.38-2.45)	0.94
High: ≥167	50 (45.9)	10 (12)	7.33 (2.80-19.24)	<0.001	3.60 (1.23-10.53)	0.019
Cholesterol (mg/dl)						
Low: <168	40 (36.7)	18 (21.7)	2.91 (1.43-5.94)	0.003	2.91 (1.08-7.85)	0.03
Medium: ≥168 and <200	44 (40.4)	25 (30.1)	3.73 (1.74-8.00)	0.001	3.03 (1.09-8.41)	0.03
High: ≥200	25 (22.9)	40 (48.2)	1 (-)		1 (-)	
Neutrophils (per µl)						
Low: <4007	22 (20.2)	45 (54.2)	1(-)		1 (-)	
Medium: ≥4007 and <5955	42 (38.5)	25 (30.1)	3.35 (1.65-6.84)	0.001	2.95 (1.14-7.60)	0.02
High: ≥5955	45 (41.3)	13 (15.7)	7.08 (3.18-15.77)	<0.001	4.90 (1.60-14.94)	0.005

OR: odds-ratio; 95%CI: confidence interval of a 95%; A1AT: alpha 1-antitripsin; [a] OR adjusted by age and gender; [b] OR adjusted by age, gender, alpha 1-antitripsin, cholesterol and neutrophils.

High neutrophil and A1AT levels and low cholesterol levels were the only significant variables in the multivariate analysis. Therefore, those were the variables chosen for their stratification in terciles and their inclusion in the score. It can be observed that three variables are associated significantly with the probability of being a case: patients with LC+COPD had significantly higher levels of neutrophils [OR 4.90 (95%CI 1.60-14.94 for those in the highest tercile of neutrophils, p=0.005] and A1AT [OR 3.6 (95%CI 1.23-10.53), for those in the highest tercile of A1AT, p=0.019] and lower cholesterol levels [OR 2.91 (95%CI 1.08-7.85), for those in the lowest tercile of cholesterol, p=0.03] than COPD controls. The point scoring system shown in Table 5 was used to measure the magnitude of the association of each of the significant factors in the multivariate analysis with the odds of being a case, thus leading to the development of a risk score.

Table 5. Point scoring system for predicting the risk of being a case.

Characteristic	Points assigned*
High A1AT levels (≥167 mg/dl)	4
Low and medium cholesterol levels (<200 mg/dl)	3
Medium neutrophil levels (≥4007 and <5955 per µl)	3
High neutrophil levels (≥5955 per µl)	5

*A total point score for a given patient is obtained by summing all the points for each applicable characteristic. The points assigned to each predictor variable were based on coefficients obtained from the logistic-regression model adjusted for age, sex, alpha 1-antitripsin, cholesterol and neutrophils exposed in Table 4.

Performance and ROC curves of this risk score are presented on Figure 2 and Table 6. Based on our model and assuming a prevalence of 25% among COPD patients, we reached a sensitivity of 80%, with an optimal negative predictive value (NPV) of 90.7%[7].

Figure 2. ROC curve of the risk score.

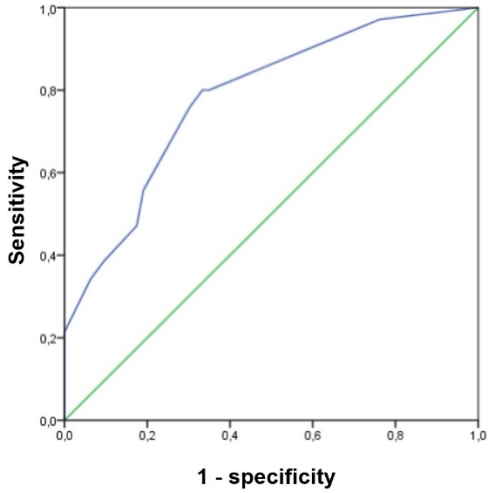

Table 6. Sensitivity, specificity and predictive values of the risk score.

	AUC (95%CI)	Cut-off value	S (%)	Sp (%)	PPV (%)	NPV (%)
Risk score*	0.78 (0.71-0.86)	>3.5 points	80	65.1	43.5	90.7

* The points assigned to each predictor variable were based on coefficients obtained from the logistic-regression model adjusted for age, sex, alpha 1-antitripsin, cholesterol and neutrophils; S: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value, AUC: area under the curve; CI: confidence interval

We repeated the univariate and multivariate analyses excluding patients with advanced LC stage, to minimize the effect of higher inflammation levels in this kind of tumours. We found that in local LC+COPD, A1AT was significantly higher than in COPD patients: OR 1.02 (1.00-1.03); p=0.03, with an AUC of 66.4 (Table 7).

Table 7. Analysis in patients with local LC.

UNIVARIATE ANALYSIS			
	Cases (localized LC+COPD)	**Controls (COPD)**	**p**
Baseline characteristics			
Gender (male), n (%)	31 (83.7)	65 (78.3)	0.330
Age, mean (SD)	65.5 (12.9)	64.6 (9.4)	0.680
BMI, mean (SD)	27.7 (4.3)	27.3 (4.5)	0.510
Laboral exposure, n (%)	15 (40.5)	25 (30.1)	0.390
Tobacco history, n (%)	37 (100)	82 (98.8)	0.690
Active smokers, n (%)	20 (54.1)	45 (54.2)	0.340
Pack-years, mean (SD)	45.9 (24)	47.5 (25)	0.750
GOLD I-II, n (%)	5 (13.5)	66 (79.5)	0.260
GesEPOC A (%)	35 (94.6)	80 (96.4)	0.490
Bodex, mean (SD)	0.9 (1.50)	0.8 (1.2)	0.700
CAT, mean (SD)	8.5 (3)	9.7 (7.6)	0.570
FEV_1(%), mean (SD)	71.6 (21.3)	71 (20.2)	0.880
DLCO(%),mean (SD)	72.6 (22)	70.4 (22.6)	0.660
Charlson index, mean (SD)	1.3 (1.9)	0,7 (1)	0.010
Inflammatory markers			
TNF-α (pg/ml), mean (SD)	11.6 (21)	9.3 (7.4)	0.530
IL-6 (pg/ml), mean (SD)	6.5 (6.1)	6.2 (12.1)	0.850
IL-8 (pg/ml), mean (SD)	22.1 (46.4)	19.2 (28.8)	0.740
Leukocytes (per µl), mean (SD)	8,880.9 (4,039.1)	7,706.1 (2,334)	0.110
Lymphocytes (per µL),mean (SD)	2,744.9 (3,190.1)	2,398.5 (965.7)	0.370
Neutrophils (per µl), mean (SD)	5,491.1 (2,324.7)	4,464.2 (2,136.7)	0.020
NLR, mean (SD)	2.9 (1.9)	2.1 (1.5)	0.030
Platelets (per µl), mean (SD)	273,594.6 (132,871.4)	243,402.4 (72,978.9)	0.270
MPV (fl), mean (SD)	8.4 (1.3)	8.9 (1)	0.040
PLR, mean (SD)	135 (76.3)	118.5 (72.1)	0.260
Fibrinogen (mg/dl), mean (SD)	395.3 (185.2)	392.5 (166.5)	0.950
A1AT (mg/dl), mean (SD)	157.9 (42.6)	136.8 (29.1)	0.030
IgE (kU/l), mean (SD)	176.5 (216.5)	177.8 (569.3)	0.990
CRP (mg/l), mean (SD)	14.7 (20.6)	6.1 (8.8)	0.009
Cholesterol (mg/dl), mean (SD)	180.1 (44.6)	201.8 (37.1)	0.010
Bilirrubin (mg/dl), mean (SD)	0.73 (0.50)	0.6 (0.2)	0.060
MULTIVARIATE ANALYSIS			
	OR	**95%CI**	**p**
A1AT (mg/dl)	1.02	1.00-1.03	0.03

BMI: Body mass index; GOLD: Global Initiative for Obstructive Lung Disease; GesEPOC A: non exacerbators, according to the Spanish Guidelines of COPD; CAT: COPD Assessment Test; FEV1: forced expiratory volume in the first second; DLCO: carbon monoxide diffusion capacity; IL: interleukin; NLR: neutrophil/lymphocyte ratio; MPV: mean platelet volume; PLR: platelet/lymphocyte ratio; A1AT: alpha 1-antitripsin; IgE: E immunoglobulin, CRP: C reactive protein.

Discussion

Our results suggest that a panel of 3 biomarkers out of a panel of 16, which are easy to assess, might be able to detect LC in patients presenting COPD. As we have previously stated, evidence suggests that COPD is a risk factor for developing LC[7], and one of the underlying mechanisms described is inflammation. Chronic inflammation has long been associated with

carcinogenesis, contributing to 25% of all human cancers[8]. We have observed that neutrophils, A1AT and cholesterol are associated with the risk of LC in COPD patients, and if they are used combined, they might predict LC risk with an AUC close to 80 %. If confirmed in other studies, these results could be relevant since LC is frequent among COPD patients and their use might detect the disease in earlier stages predicting a better clinical outcome.

Evidence suggests that COPD is a risk factor for developing LC[7], and one of the underlying mechanisms described is inflammation. Chronic inflammation has long been associated with carcinogenesis, contributing to 25% of all human cancers[8] and systemic inflammation has also been shown to be a relevant manifestation of COPD[25].

As previously exposed in Table 1, several markers have shown associations with both COPD and LC. Leukocytes, TNF-α, IL-6, IL-8, cholesterol, bilirubin and fibrinogen levels increase mortality in COPD patients, whereas white blood and platelet markers are associated with a risk of COPD exacerbations[10,11,26-28]. Also, elevated IgE levels can be found in COPD patients[29]. In addition, TNF-α, IL-6, IL-8, NLR, PLR, IgE have been associated with LC risk in healthy subjects, being IL-6, lymphocytes, neutrophils, NLR, platelets, PLR, fibrinogen, A1AT, CRP and bilirubin poor prognostic factors in LC patients[11,14,30-32]. According to our results (Figure 1), we found differences in marker levels in patients with LC+COPD, and even in LC patients without COPD, such as IL- 6, leukocytes, PLR, fibrinogen, neutrophils, NLR, platelets, A1AT and CRP. This may indicate that these markers seem to be more related to the existence of LC than to COPD itself.

In the multivariate analysis we found that some markers were statistically associated with LC onset: higher levels of neutrophils and A1AT and lower cholesterol levels.

Lymphocytes play a crucial role in the cell-mediated host immune response to tumors. Infiltration of tumors by lymphocytes correlates with better prognosis in some cancers, although disease progression is associated with high leukocyte and neutrophil count[11]. Neutrophils support angiogenesis by secreting proangiogenic factors or proteolytic activation of such factors. Also, they ensure the collection of epidermal growth factor (EGFR), transforming growth factor-β1 (TGF- β1), platelet-derived growth factors that contribute to tumorigenesis. Neutrophils contain both pro- and anti-tumor subpopulations[11]. Neutrophil counts are known to

be an independent indicator of poor prognosis in LC patients, whereas low neutrophil counts are associated with longer survival[33].

Most of the literature available on the relationship between A1AT and COPD or LC focuses on the deficit of this protein[34]. However, its role as an inflammatory marker when it presents high levels has been less studied. Possible carcinogenic mechanisms have been suggested from the excess activity of neutrophil elastase[34], which induces tissue damage at the pulmonary level due to a protease-antiprotease imbalance. More studies are needed to establish if there is an association between the A1AT and LC risk. Nevertheless, there is evidence that A1AT promotes lung adenocarcinoma metastasis[13].

Although hyperlipidemia is a negative prognostic factor in patients with stomach and prostate cancers, very few studies have explored the significance of this in LC. In one trial, HDL, LDL and total cholesterol levels were lower in LC patients when compared with healthy controls, although only HDL levels were prognostically significant[11]. The observed results of cholesterol levels in this study has not shown to be related to statin consumption or to the presence of cachexia.

In this study, we provide a risk score for COPD patients with higher risk of CP, achieving high sensitivity and NPV. In fact, the area under curve is close to 80%, and therefore only 20% of patients using this score would be misclassified. Our approach involves the measurement of A1AT, neutrophils and cholesterol to generate a classification score for each individual to predict LC. Although we did reach high sensitivity and NPV, specificity and positive predictive value were modest. This was expected since the alteration of any of the selected markers is not specific for LC, given that they are markers that show high heterogeneity among patients, that they can be modified by the different comorbidities, and that there is an important variability that it is shown in the size of some of the confidence intervals[35].

We repeated the analyses in patients with COPD and localized LC, in order to minimize biases due to higher inflammation levels in patients with advanced LC, given that patients with local LC would be the objective in the case of an eventual LC screening. In this case, the only parameter which was significantly higher in patients with LC+COPD was A1AT, although the number of patients in the group of cases was considerably reduced (37 patients), which limits

the conclusions that can be drawn from this subgroup of patients. It is therefore pending if this panel results are maintained when using LC patients at an early stage presenting COPD.

The use of risk prediction models may inform selection of subjects most likely to benefit from computed tomography screening; and risk markers such as A1AT, neutrophils or cholesterol may provide useful risk information in addition to questionnaire information on tobacco exposure history. Inflammation markers are unlikely to provide enough added risk information on their own, but in combination with other risk markers they may be useful for risk stratification.

Regarding LC characteristics, the most frequent histological type was adenocarcinoma, which goes in line with other studies[5]. SCLC was significantly higher in LC+COPD patients and there was a trend, although not significant for squamous LC in this group of patients. This study found that smoking had a significantly higher effect on the SCLC risk of COPD subjects, compared with non-COPD subjects[36]. Also, COPD status was independently associated with SCLC risk when adjusted for age, gender, and smoking. Squamous LC was also more frequent in smokers and has been associated with the presence of emphysema[37].

Our study shows several limitations, inherent to its case-control design. The number of controls (COPD) is slightly lower than the number of cases (LC+COPD), although we have a second control group of patients with LC without COPD. Furthermore, the score created should be classified as exploratory, though it has relatively high discrimination power. It must be validated against other cohorts of patients from other settings. On the positive side, study groups are very similar regarding gender and age distribution. In addition, there are limitations derived from the nature of the markers that, as previously discussed, are not very specific and may present a great inter and intraindividual variability.

Our study also presents a series of advantages. This is the first work analyzing a panel of 16 blood markers in a subgroup of patients with underlying COPD, with adjustments by stage, histological type, emphysema and smoking. Also, we added a second control group of patients with LC, to show that some markers are more related to the existence of LC than to COPD itself. Most patients presented with a mild COPD. This is useful, as they represent the group most likely to benefit from more aggressive approaches of a malignancy. On the other hand, a very complete collection of variables was made, and the sample size is very acceptable. The whole

Galician population has public health coverage, meaning there was no selection bias for our sample as we recruited more than 95% of all LC cases diagnosed in the referral area during the study period. We must consider that, despite a reasonable but modest sample size, we have included in the logistic regression model five variables of which three remained statistically significant, regardless of sex and age, which is why they are good predictors of the risk of being a patient with LC and COPD, which makes our results relevant. In addition, our risk score comprises only 3 parameters which may be analyzed routinely. This makes our risk score simple and affordable, and it may prove useful at guiding decision-making in clinical practice, such as whether to implement a LC screening system for at-risk patients, or even modify the probability of malignancy scales when evaluating a pulmonary nodule.

In conclusion, patients with COPD who also suffer from LC have higher levels of A1AT and neutrophils and lower cholesterol. These markers seem to be more related to the presence of LC than to COPD itself, since they are increased in patients with LC without COPD. In patients with LC+COPD at localized stage, A1AT is significantly higher. The combination of A1AT, neutrophils and cholesterol in the risk score variable presents a high sensitivity and NPV, so it can be a useful tool when identifying patients with LC+COPD. However, although sensitive, these markers are not specific of LC, and more studies are needed to inform selection of COPD subjects most likely to benefit from computed tomography screening or selection of nodules at higher risk of being malignant, as risk markers such as A1AT, neutrophils and cholesterol may provide useful risk information in addition to clinical questionnaires.

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CHAPTER 9.

DISCUSSION.

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9.1. DISCUSSION: HYPOTHESIS AND METHODS

The poor prognosis of LC, its high prevalence among patients with COPD and the evidence postulating COPD as a risk factor for LC development (3,12), make it necessary to develop strategies with a potential use in the early detection of LC in patients with COPD and/or emphysema. Therefore, it is essential to improve our knowledge of the interaction between LC and COPD, and also to establish whether there is any relationship between the type of pulmonary emphysema and the development of LC. In addition, this would have prognostic and therapeutic consequences and would even have implications on the implementation of screening strategies. However, until now, it is not recommended to carry out a general screening of LC, although it is true that there are more and more working groups evaluating this point (206,207). The reasons why LC screening has not started yet in our environment are the low positive predictive value of LC screening by CT, the important implications that false positives may have for patients, the possibility of overdiagnosing cases of LC, the risks of developing radiation-induced cancer, and the great economic and organizational impact that a CT screening of the entire smoking population would imply (208). That is why, so far, there is no consensus about its realization in Europe. Some international guidelines, such as the IASCL, the ACCP, the ASCO or the ATS (209) recommend the implementation of screening strategies, while the Spanish and European guidelines are more inclined to recommend strategies based on the early detection of LC. These guidelines place special emphasis on the role played by the LCRDU within a multidisciplinary approach, as well as case-management nurses, having both demonstrated their capacity to minimize the loss of LC cases, accelerating the times of diagnosis and also reducing the costs of the high number of patients who previously required hospital management (3,12).

Recently, numerous studies have been published that seem to show the existence of a relationship between LC, COPD and emphysema (15,60,65). However, there are no studies focusing on the phenotypic and multidimensional characterization of cases of COPD with LC that can help us choose the most appropriate therapy and its prognosis. The possibility of a relationship between different types of emphysema and the existence of LC has not been studied either. Similarly, there is little evidence about the role of some markers of inflammation in blood, which could serve as tools for early diagnosis, possible LC screening, severity assessment, evaluation of therapeutic response and/or taking diagnostic and therapeutic

decisions in the subgroup of patients with COPD. As a result of the limited information available on the relationship between these entities, this research project was carried out.

The aim of this thesis is to estimate COPD prevalence and its degree of underdiagnosis in patients with LC, as well as to evaluate the clinical profile of patients with COPD and LC comparing it with another control group of patients with COPD without LC, to analyze its phenotypic, radiological and multidimensional characterization, considering the little existing literature and its discrepant results.

With this purpose, several studies were designed. Initially, a systematic review of the evidence available to date was conducted. Subsequently, a prospective cohort study was designed for descriptive purposes of the frequency and phenotypic characteristics of patients synchronously diagnosed with COPD and LC, followed by two observational case-control studies, in which the cases were patients with COPD and LC, and controls, patients with COPD without LC. The cohort study was designed with the objective of establishing the prevalence and underdiagnosis of COPD in patients with LC, due to the high underdiagnosis of COPD in the general population. For this same reason and based on the need to have a CT for all patients with COPD, the second and third studies presented a case-control design, because it would have been very long and complex to conduct a cohort study designed to establish a relationship between the type of emphysema and the development of LC, or to study the role of different biomarkers by subgroups.

The fact that the initial cohort study was multicentric has allowed to reach a large sample size, therefore including a representative sample of the resident population in the geographical area in which the research was developed, given that the entire Galician population has access to public healthcare coverage, which allows recruiting more than 95% of the total LC of the respective health areas.

9.2. DISCUSSION: RESULTS

The first cohort study included 602 patients with LC, 310 with LC and COPD and 292 LC without COPD. The second case-control study included 243 patients, 169 with LC and COPD and 74 with COPD without LC. The third study included 280 patients, 109 cases with LC and COPD, 83 controls with COPD and 88 cases of LC without associated COPD.

Most patients included in the studies were male. As explained in the introduction, over the last decades, the male/female ratio of LC has been evolving from 10/1 to approximately 4/1 at present, mainly due to the incorporation of women into tobacco consumption (16,17). In the LC and COPD group, 88.7% of the cases were male, with a 7/1 ratio. This is explained not only by the existence of LC, but also of COPD, since it is a disease that affects mostly men (41). In the LC group without COPD, the ratio was 2/1, lower levels than those described for LC in the general population, which could be explained by a higher proportion of women within the group of non-smokers, who are mostly in the group that does not suffer from COPD (16,17).

The mean age of our patients (67 years) is slightly lower than that described for LC in the literature (3), although it is true that the subgroup of patients with LC and COPD has almost the same age. Perhaps the age described in the literature is interfered by the presence of COPD, since, if we assume that COPD is a risk factor for the development of LC, it would require a latency period prior to the diagnosis of the neoplasm. This would explain the fact that patients with LC without COPD are younger.

As described in the literature, most LC diagnoses are performed in advanced stages, which implies a low survival at 5 years. In our work, LC diagnosis (with or without associated COPD) was performed in advanced stages in more than half of the cases, without significant differences between having a concomitant COPD or not. Because the follow-up time of our cohort study was low (2 years), we could not draw definitive conclusions about the implications of this fact on survival. However, we did observe that the median survival of patients with LC without COPD was 37% higher than that of LC patients with COPD, although not significantly. However, both survival medians were quite low (22 and 16 months respectively).

COPD prevalence among patients with LC was 51.5%, with a previous diagnosis of COPD in 28.4% cases. This shows that COPD is a common comorbidity among patients with LC, showing similar data to other studies available in the literature (56,210,211). The high percentage of COPD underdiagnosis is striking: 71.6%, which shows similar levels to those found in the general population. This means that, despite the availability of national and international guidelines, COPD remains an entity with a high degree of underdiagnosis, also in patients with LC. This may mean a worse response to treatment in patients with LC and COPD, due to delays in diagnosis and the influence of COPD when conditioning the evolution and therapeutic options in these patients (5).

As previously discussed, tobacco is the main risk factor for developing COPD, emphysema and LC (81,177). Practically all (98%) patients with COPD (with or without LC) had some type of previous exposure to tobacco, being almost half of them active smokers. These results were expected, since smoking is practically a necessary condition to diagnose a patient with COPD, except in those cases with other types of exposures (in our case, exposure to biomass smoke). More than 70% of patients with LC without COPD had presented some type of exposure to tobacco smoke, with 45.7% of cases still being active smokers. This clearly supports the evidence that postulates smoking as the main risk factor for both diseases.

In both studies, patients were frequently mild COPD and were non-exacerbators (in the cohort study, 73.9% were GOLD I-II and 76.9% GOLD A-B, with a 90.3% of non-exacerbators; that, in the case-control study, 69.8% were GOLD I-II and 90% GOLD A-B, with a 90.1% of non-exacerbators). These data are relevant, because this is the group of patients with COPD that we are most interested in characterizing, given that their functional situation may allow them to benefit from diagnostic strategies, extension evaluation and more aggressive therapies against their oncological pathology. In addition, there is evidence that the risk of developing LC and dying from it is greater in patients with COPD GOLD I-II, while patients with more advanced COPD are more likely to die from COPD itself (5) .

Adenocarcinoma was the most frequent histological type overall in all the studies included in this thesis. This may be related to several factors, such as changes in the characteristics of cigarettes (with filter and low nicotine), changes in the classification of adenocarcinoma (currently classified as adenocarcinoma to bronchiole-alveolar carcinoma), the increase in casual diagnoses (since adenocarcinoma is a more peripheral tumor and takes longer to produce symptoms) and the increase in women with LC, due to their greater susceptibility to develop malignancy after genetic, hormonal, and mutational factors, with a higher risk of having EGFR mutations (17-20).

The subgroup of patients with LC and COPD had more frequently squamous cell carcinoma and SCLC, when compared with patients with LC but without COPD. In addition, we found that squamous carcinoma was the most frequent diagnosis in localized stages, while in advanced stages the most frequent histological type was SCLC. These data are similar to those available in the literature (22,212,213). Both histological types have been associated with smoking, more frequently than in the case of adenocarcinoma. In addition, the presence of

squamous cell carcinoma was more significantly associated with the presence of emphysema, and in our series, patients with LC and concomitant COPD had a lower DLCO, which could indicate the existence of an associated emphysema and thus relate to a higher prevalence of squamous carcinoma (162).

Patients with LC and COPD had more comorbidities measured by the Charlson index than patients with LC without COPD, which could be explained by several factors. Cases with LC and COPD had a higher prevalence of smoking, which could imply the presence of chronic inflammatory processes that would lead to the development of a greater variety of comorbidities. In addition, it is known that apart from systemic inflammation, there are other mechanisms that may influence the coexistence of COPD with other cardiac and metabolic comorbidities, such as cellular senescence or telomeric shortening (28,29,214-217).

Patients with LC and COPD were older and thinner than patients with COPD without LC. The higher age could be due to the latency time necessary for COPD to lead to the development of LC, while a lower BMI could be related to the fact that the majority of cases were non-exacerbating patients with emphysema.

As previously explained, the available evidence about the association between the presence of emphysema and the development of LC is weak, especially given the disparity of results published to date, although it does seem clear that the evaluation by specialized radiologists of the existence of emphysema can be better correlated with the development of LC than its detection by automatic systems (60,65,179). In this work, we did not find a significant association between the existence of emphysema (considering all the subtypes together) and the presence of LC, despite having performed the evaluation of this emphysema in a semiquantitative manner by four experienced radiologists. However, in the literature available to date, there are no data that separately analyze the different types of emphysema, which could mean that the distribution between forms of emphysema within each study is heterogeneous and that this may therefore contribute to the disparity of the results. As explained below, an association between a specific subtype of emphysema and the presence of LC was found in this project.

The second study focused on analyzing the existence of a relationship between a specific type of emphysema and the existence of LC. An association was observed between paraseptal

emphysema (alone or combined) and the presence of LC in patients with COPD. It is known that paraseptal emphysema affects predominantly upper lobes (185,186), something that is also observed in the present work. It is associated with male sex, an older age and the existence of interstitial pathology as well (162,186). In fact, it is the most common type of emphysema found in the association of emphysema and fibrosis (162,186). It is a type of emphysema that is not usually clinically relevant until it is in advanced stages, having not demonstrated a relationship with the development of symptoms in COPD, nor with the degree of airflow obstruction, nor with smoking history (162,187). In the emphysema study, a subgroup analysis was performed comparing the characteristics of patients with paraseptal emphysema with those of the other types of emphysema, finding a higher prevalence of adenocarcinoma, which could be related to the fact that it is a peripheral tumor that, as in the case of paraseptal emphysema, presents later clinical manifestations (2).

De Torres et al. (80), described a scale (the COPD-LUCSS-DLCO), designed to help identify those patients with a high risk of developing LC. It is a scale that divides patients into two risk groups based on a score obtained from the combination of their age, BMI, smoking status and DLCO. In the study by De Torres, patients in the high-risk group were 2.4 times more likely to die than patients in the low-risk group. In the present project, 78.2% of the patients with LC and COPD would have been assigned to the high-risk group according to this scale, compared to 57.1% of patients with COPD without LC. However, this scale still needs to be validated.

In the third study, a 16-biomarker panel was analyzed in three groups of patients: COPD, LC and LC with concomitant COPD. The results of this study show that patients with COPD who also have LC have higher levels of neutrophils and A1AT and lower cholesterol levels.

Neutrophils promote angiogenesis by secreting proangiogenic factors. In addition, they intervene in the routes of EGFR, transforming growth factor-β1 (TGF-β1) and growth factors derived from platelets, thus contributing to tumor genesis (218). It is known that neutrophil counts are independent indicators of poor prognosis in patients with LC, whereas low neutrophil counts are associated with longer survival (195).

Most of the data that relate the A1AT protein to COPD or LC are focused on its deficit (121). However, its role as an inflammatory marker when it is elevated has not been studied in this context. On the other hand, although more studies are needed to establish if there is an

association between A1AT and LC risk, there is evidence that A1AT promotes metastasis of lung adenocarcinoma (197).

Although hyperlipidemia is a poor prognostic factor in patients with stomach and prostate cancer, there are few studies evaluating its role in LC. In this work (218), HDL, LDL and total cholesterol levels were lower in patients with LC compared with healthy controls, although only HDL levels were statistically significant.

In the study of biomarkers, a risk scale was also developed to predict which patients with COPD had a higher risk of belonging to the group of cases (patients with COPD and LC), achieving high sensitivity and NPV. In fact, the area under the curve is close to 0.80 and, therefore, only 20% of patients using this score would be classified incorrectly.

Therefore, A1AT, neutrophils and cholesterol are presented as parameters with potential diagnostic utility in the study of a possible LC in patients with COPD. However, although these are sensitive markers, they are not specific to COPD or LC, so our findings provide the basis for further studies that allow us to select those subjects with COPD who are more likely to benefit from screening by CT, as well as being able to select nodules with a higher risk of being malignant.

9.3. Advantages of this thesis

This thesis started with a systematic review, which involved an exhaustive search of available literature on the relationship between COPD, emphysema and LC, which minimized the loss of relevant results. This review, published in a first-quartile journal, showed that both COPD and emphysema increase the risk of LC, with a dose-response association with tobacco. In addition, the results show that COPD is a highly underdiagnosed disease among patients with LC. After the systematic review, three studies were carried out, one of cohorts and two of cases and controls, with the main novelty that previously there were few data about the clinical and functional characteristics of patients with LC and COPD, as well as null information about the comorbidities that this group of patients usually presents. A total of 956 patients were included, which implies a reasonably large sample size, and the fact that the public health system is universal in our country, and that the Pneumology services of Vigo and Ourense have a LCRDU that evaluates the 95 % of all LCs in both health areas, has minimized the loss of cases and thus obtain a sufficiently representative sample of the southern area of Galicia. On the other hand, the diagnosis of COPD was made based on clinical and spirometric criteria in all cases, in accordance with the recommendations of current national and international guidelines (29,42),

being another novelty of this work the multidimensional characterization of patients with COPD who also have LC. In addition, it is the first work that analyzes the possibility of a relationship between a specific type of emphysema and the existence of LC and also the first to analyze the impact of a broad panel of 16 biomarkers when stratifying patients in the group of cases and controls.

All the data collected in the clinical history, as well as the procedures performed and analyzed are of quality, carried out by highly trained personnel, with specific training in pulmonary function, clinical analysis, thoracic radiology and pathology, with areas of maximum complexity accredited at national level and with a LCRDU that has shown to significantly reduce the delay times in LC diagnosis, with a high diagnostic accuracy and a high degree of satisfaction for patients.

The study designs carried out are adequate, given that the cohort and case-control studies are robust observational studies to establish cause-effect relationships. The design of cohorts for the group of patients with LC allowed us to prospectively identify those patients who also had concomitant COPD, a key aspect due to the high rates of underdiagnosis of this disease. This has made it possible to establish more clearly the prevalence of COPD and the degree of underdiagnosis in the cohort of patients with LC. The design of cases and controls for the second and third studies in the group of patients with COPD presents some limitations inherent to their case-control nature. However, they are also suitable for the study performed, allowing us to review LCs quickly and without a latency period, given that a cohort design would have been more complex, expensive and long.

9.4. LIMITATIONS OF THIS THESIS

The main limitation of the systematic review carried out is the heterogeneity of the studies included in it, which did not allow the realization of a meta-analysis. Regarding the cohort study, the period of patient follow-up was relatively short (2 years), which did not allow to draw definitive conclusions about the implications on survival.

The main limitation of the second study (cases and controls), in addition to those derived from this type of design, was the difference between the number of cases and that of controls (because the controls had to be patients with recently diagnosed COPD) and also the fact that emphysema was evaluated by several expert radiologists, which can imply certain subjectivity,

although it is true that the literature establishes a good inter and intra-observer correlation when evaluating the type of emphysema (Kappa 0.70) (219).

The main limitations of the third study (cases and controls) are that the number of controls (COPD) is slightly lower than the number of cases (COPD and LC), although a second control group of patients with LC without COPD is provided. In addition, the risk scale requires its validation in other studies, although it is true that it has a relatively high discriminatory power. There are also limitations derived from the nature of the markers that, as already explained, are not very specific and can present a great interindividual and intraindividual variability.

9.5. IMPLICATIONS

The present work presents new information about the characterization of patients with COPD and LC. Although adenocarcinoma was the most frequent histological type, patients with LC and COPD are more frequently squamous carcinomas and have a lower carbon monoxide diffusing capacity. This could suggest a relationship between the existence of smoking, emphysema and the presence of squamous carcinoma. On the other hand, patients with LC and COPD were, in general, milder COPD and with fewer exacerbations, which could imply changes in the follow-up of these patients, especially in those cases with associated emphysema. In addition, COPD is a prevalent and highly underdiagnosed disease in patients with LC, so greater efforts should be made to make an early diagnosis of COPD and select patients with an increased risk of developing LC.

The fact that paraseptal emphysema in patients with COPD is more frequent in the subgroup of patients who also have LC, implies that patients with COPD and this type of emphysema could constitute a risk group for the development of LC, especially the subtype adenocarcinoma. These results justify exploring the benefit of performing interventions to prevent or detect LC in patients with COPD in which the presence of paraseptal emphysema has been observed, supporting the benefit of performing thoracic CT in those patients with COPD who are suspected of having emphysema.

On the other hand, the results on the A1AT, neutrophils and cholesterol (alone or combined in a scale), obtained in the third work allow to lay the foundations to be able to carry out more studies that make it possible to select those subjects with COPD with a greater probability of benefiting from screening by computed tomography, as well as being able to select nodules at

higher risk of being malignant, with a combination of clinical parameters, risk exposures, pulmonary function, radiology and blood analysis.

9.6.FUTURE

The results shown in the works included in this thesis are part of a national multicenter project, included in the *Proyecto Integrado de Investigación en Oncología Torácica* (PII) of the *Sociedad Española de Patología Respiratoria* (SEPAR). This has enabled the development of the four articles that constitute this thesis (the systematic review, the cohort study and the two case-control studies).

The two most novel findings in the works included in this thesis are that paraseptal emphysema in patients with COPD is more frequent in the subgroup of patients who also have LC, especially within the adenocarcinoma subgroup, and that high levels of A1AT and of neutrophils and decreased of cholesterol, are associated with a higher probability of presenting LC in patients with COPD. In fact, the study of biomarkers has allowed us to develop a risk scale that has shown high sensitivity and NPV, with an area under the curve (AUC) close to 0.80.

Considering these results on paraseptal emphysema and blood biomarkers, this project will try to continue with several multicentric works at a national level. These studies will be designed to prospectively validate our results, with the aim of proposing a combined scale of clinical parameters, risk exposures, pulmonary function, type of emphysema and blood markers, to select those patients with COPD most likely to be the target population in LC screening strategies. As a secondary objective, we intend to modify the predictive scales of malignancy in the study of pulmonary nodules and other suspicious lesions of LC in patients with COPD.

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CHAPTER 10.
CONCLUSIONS.

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1. According to the literature analyzed in our systematic review, both COPD and emphysema increase the risk of developing LC, being this risk higher for smokers and increasing with higher tobacco consumption. These entities share several underlying etiopathogenic mechanisms.

2. In the multicenter cohort study, it was found that COPD is a highly underdiagnosed disease, also among patients with LC. The analyzes carried out in this work and in the systematic review emphasize the need to perform spirometry in active and former smokers, as well as imaging tests, in order to diagnose COPD and emphysema correctly and early, thus being able to select patients with an increased risk of developing LC.

3. Patients with LC and COPD present more squamous cell carcinomas and lower DLCO than patients with LC without COPD. This suggests a relationship between squamous cell carcinoma, smoking and the presence of emphysema.

4. Patients with LC and COPD have more comorbidities than LC patients without COPD, which could be related to the high prevalence of smoking in these patients, in addition to COPD itself.

5. Paraseptal emphysema in patients with COPD is more frequent in those cases that also have LC. In addition, patients with paraseptal emphysema have a higher proportion of adenocarcinoma cases than other types of emphysema. Therefore, patients with COPD and paraseptal emphysema could be a risk group for LC development, especially adenocarcinoma.

6. Patients with COPD who also have LC have higher levels of A1AT and neutrophils and lower cholesterol levels. These markers seem to be more related to the presence of LC than to COPD itself, since they are increased in patients with LC without COPD. On the other hand, in patients with LC and COPD at localized stage, A1AT is still significantly higher. In addition, the combination of A1AT, neutrophils and cholesterol presents a high sensitivity and NPV, so it may be a useful tool to identify patients with LC and COPD. However, although they are sensitive, these markers are not LC specific, and more studies are needed

so that these biomarkers can be used in clinical practice in order to select those subjects with COPD who are more likely to benefit from CT screening, or to select those nodules or other lesions with higher risk of malignancy.

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ANNEX

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ANNEX 1. APPROVAL OF THE PROJECT BY THE GALICIAN ETHICS COMMITTEE.

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XUNTA DE GALICIA
CONSELLERÍA DE SANIDADE
Secretaría Xeral

Comité Autonómico de Ética de la Investigación de Galicia
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galicia

DICTAMEN DEL COMITÉ AUTONÓMICO DE ÉTICA DE LA INVESTIGACIÓN DE GALICIA

Paula M. López Vázquez, Secretaria del Comité Autonómico de Ética de la Investigación de Galicia

CERTIFICA:

Que este Comité evaluó en su reunión del día 15/10/2013 el estudio:

Título: EPOC y Cáncer de Pulmón: Infradiagnóstico y Caracterización Clínica
Promotor: Alberto Fernández Villar
Código de Registro CEIC de Galicia: 2013/439

Y, tomando en consideración las siguientes cuestiones:

- La pertinencia del estudio, teniendo en cuenta el conocimiento disponible, así como los requisitos legales aplicables, y en particular la Ley 14/2007, de investigación biomédica, el Real Decreto 1716/2011, de 18 de noviembre, por el que se establecen los requisitos básicos de autorización y funcionamiento de los biobancos con fines de investigación biomédica y del tratamiento de las muestras biológicas de origen humano, y se regula el funcionamiento y organización del Registro Nacional de Biobancos para investigación biomédica, y la ORDEN SAS/3470/2009, de 16 de diciembre, por la que se publican las Directrices sobre estudios Posautorización de Tipo Observacional para medicamentos de uso humano.
- La idoneidad del protocolo en relación con los objetivos del estudio, justificación de los riesgos y molestias previsibles para el sujeto, así como los beneficios esperados.
- Los principios éticos de la Declaración de Helsinki vigente.
- Los Procedimientos Normalizados de Trabajo del CEIC de Galicia

Emite un **INFORME FAVORABLE*** para la realización del estudio en los centros y con los investigadores siguientes

Centros	Investigadores Principales
C.H. Universitario de Vigo	Alberto Fernández Villar
C.H. Universitario de Ourense	José Abal Arca

**En los documentos de consentimiento incluir el nombre del investigador principal y forma de contacto en cada uno de los dos centros (CHOU y CHUVI)*

En Santiago de Compostela, a 21 de octubre de 2013
La Secretaria

Paula M. López Vázquez

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ANNEX 2.

EXAMPLE OF REGISTRATION OF THE EMPHYSEMA BY RADIOLOGISTS

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	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z
1	Código paciente	CENTROLOBULILLAR					PARASEPTAL					PANACINAR					CICATRICIAL					BULLAS				
2		LSD	LM	LID	LSI	LII	LSD	LM	LID	LSI	LII	LSD	LM	LID	LSI	LII	LSD	LM	LID	LSI	LII	LSD	LM	LID	LSI	LII
3		0	2	2	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	3	0	0	0	0
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Valores Enfisema	
0	0
1	0% --> 25%
2	25% --> 50%
3	50 % --> 75%
4	100%

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ANNEX 3.
DETERMINATION OF INFLAMMATORY MARKERS ("COPD PROFILE").

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Peripheral venous blood was collected from all patients early in the morning. The serum was obtained by centrifugation of whole blood at 3,000 g for 10 minutes. Plasma (CITRATE as an anticoagulant) was obtained by centrifugation at 3,500 g for 15 minutes at a temperature of 4°C. The serum samples used to measure the levels of IL-6, IL-8 and TNF-α were stored at -80°C until they were analyzed. The serum concentrations of IL-6, IL-8 and TNF-α were determined by validated immunoassays (IMMULITE ONE, Siemens, Germany), complete blood counts were performed using ADVIA 2120 (Siemens, Germany); and serum CRP, cholesterol and bilirubin were measured using ADVIA 2400 (Siemens, Germany). A1AT was analyzed by nephelometric assay (IMMAGE, Beckman Coulter, USA), while IgE levels were measured by fluorometric immunoassay (PHADIA 250, Thermo Scientific, USA). Fibrinogen was analyzed in the ACL TOP 700 (Werfen Company, Spain).

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ANNEX 4. EDITORIAL: LC AND COPD: UNDERSTANDING THE COMPLEXITY OF CARCINOGENESIS.

ANNEX 5.
COMMUNICATIONS ASSOCIATED WITH THIS THESIS.

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The studies that have been presented throughout this thesis have been exposed through several communications to congresses, which are detailed below:

1. Mouronte Roibás C, Leiro Fernández V, Ruano Raviña A, Casado Rey P, Ramos Hernández C, Botana Rial M, García Rodríguez E, Priegue Carrera A, Fernández García S, Fernández Villar A. Value of a scale based on biomarkers in the differentiation between patients with COPD and COPD + LC. XLV Annual Meeting SOGAPAR. Ferrol, November 2018.
2. Mouronte Roibás C, Leiro Fernández V, Ruano Raviña A, Tilve Gómez A, Rodríguez Fernández P, Caldera AC, García Vázquez-Noguerol M, Ramos-Hernández C, Fernández-García S, Fernández Villar A. COPD, type of emphysema and lung cancer. A case-control study. 51 National Congress of the Spanish Society of Respiratory Pathology (SEPAR). Palma de Mallorca, June 2018.
3. Mouronte Roibás C, Leiro Fernández V, Ruano Raviña A, Casado Rey P, Priegue Carrera A, Tubío Pérez R, Dacal Rivas D, Arnalich Montiel V, Lojo Rodríguez I, Fernández Villar A. Inflammatory markers associated with lung cancer in COPD patients. XLIV Annual SOGAPAR Meeting and XXXI Duriense Galaic Meeting. Lugo October 2017

COPD AND LUNG CANCER. UNDERDIAGNOSIS AND CLINICAL CHARACTERIZATION.

Cecilia Mouronte Roibás.

RESUMEN EN ESPAÑOL.

1. Introducción.

1.1. El cáncer de pulmón (CP).

El CP representa alrededor del 13,5% del total de tumores, siendo el segundo más frecuente en el mundo tras el cáncer de mama y el tercero tras el cáncer colorrectal y el de próstata en España. Se estima que en 2018 hubo 234.030 casos nuevos solo en Estados Unidos. En nuestro país, en el año 2017 hubo 28.645 casos nuevos de CP (el 81,5% en varones y el 18,5% en mujeres) según datos de la Asociación Española Contra el Cáncer (AECC) y de la Sociedad Española de Oncología Médica (SEOM). Además, aunque en los últimos años se ha producido una tendencia a la estabilización de la incidencia del CP en varones, se está observando un incremento en la de mujeres. La supervivencia con CP a los cinco años supera ligeramente el 18%, lo que se debe a una elevada proporción de diagnósticos en estadios avanzados, identificándose tumores en estadios localizados únicamente en el 16-22% de los casos, si bien cada vez hay una mayor cantidad de pacientes diagnosticados de CP en fases localizadas, debido a la existencia de nuevas técnicas diagnósticas, a la mayor facilidad de acceso a ellas y a la puesta en marcha de unidades de diagnóstico rápido, pudiendo llegar la supervivencia en estos casos hasta el 56,3% a los 5 años.

El CP sigue siendo una enfermedad más frecuente en varones y, de hecho, en nuestro país la relación varón/mujer con CP sigue siendo elevada (4:1), aunque inferior a la existente hace dos décadas (10:1). Debido, en parte, a la relación del CP con el tabaquismo, y a la existencia de un tiempo de latencia entre el consumo de tabaco y el desarrollo de enfermedad, el CP debuta normalmente entre los 65 y los 74 años, con una mediana de edad de 70 años al diagnóstico. La mediana de edad de los pacientes que fallecen por CP es de 72 años.

El CP no microcítico (CPNM) representa el grupo mayoritario de CP (80%), siendo los tipos histológicos más frecuentes el carcinoma escamoso y el adenocarcinoma, que suponen el 60% del total. En los últimos años, el tipo histológico más frecuente está siendo el adenocarcinoma, debido a los cambios en la clasificación del adenocarcinoma, al aumento de diagnósticos casuales por los avances en el radiodiagnóstico, a los cambios en las características de los cigarrillos (con filtro y bajos en nicotina) y al incremento de mujeres con CP, un hecho que podría estar en relación con una mayor susceptibilidad a padecer la enfermedad por factores genéticos, hormonales, y mutacionales. Dentro del 20% de CP restantes, algo menos del 10% son carcinomas de célula grande, cuyos tratamientos sistémicos son superponibles a los del CPNM.

El cáncer pulmonar microcítico (CPM), representa en torno al 15% de los tumores torácicos, presentando un pronóstico en general desfavorable.

A pesar de que el CP sigue siendo una enfermedad con mal pronóstico, cada vez son más las series que diagnostican pacientes en estadios más localizados. Ello puede deberse a distintos motivos: cada vez se realiza un mayor número de diagnósticos en pacientes asintomáticos, porque han mejorado las técnicas de imagen y el acceso a las mismas, y porque cada vez es más frecuente que otras patologías requieran seguimiento por imagen en el que se detecta casualmente un CP. Además, en muchos centros se han implementado unidades de diagnóstico rápido y sistemas de aviso de radiólogos a neumólogos ante estudios torácicos sospechosos de malignidad, y, por otra parte, también ha mejorado significativamente la estadificación mediastínica con nuevas técnicas poco invasivas como la ecobroncoscopia (EBUS), lo que ha permitido diagnosticar a menos pacientes de afectación ganglionar metastásica basándose únicamente en estudios de imagen.

1.2. Enfermedad pulmonar obstructiva crónica (EPOC).

La EPOC se define como una enfermedad respiratoria caracterizada por una limitación crónica al flujo aéreo que no es totalmente irreversible. Se suele presentar inicialmente en forma de disnea y su curso es progresivo, siendo su principal factor etiológico la exposición al tabaco. De acuerdo con su definición, para su diagnóstico será necesario establecer el antecedente de exposición y además una espirometría obstructiva (cociente FEV1/FVC<0,7 o inferior al límite inferior de la normalidad-LIN) sin reversibilidad tras realizar una prueba broncodilatadora. De forma general, la prevalencia de la EPOC está estrechamente ligada a la prevalencia de tabaquismo, aunque en muchos países, vendrá condicionada por la exposición a otros agentes nocivos. Se espera que la prevalencia de la enfermedad aumente en las próximas décadas, debido a la exposición continuada a factores de riesgo y al envejecimiento de la población. El estudio más importante realizado en nuestro país para determinar la prevalencia de la EPOC fue el EPI-SCAN, en el que participaron Barcelona, Burgos, Córdoba, Huesca, Madrid, Oviedo, Sevilla, Requena (Valencia), Vic (Barcelona) y Vigo (Pontevedra). La prevalencia de EPOC fue del 10,2% (15,1% en hombres y 5,7% en mujeres), existiendo un elevado grado de infradiagnóstico de la enfermedad (73-78%), por lo que, teniendo en cuenta los resultados del EPI-SCAN, según la prevalencia calculada, más de 1.595.000 españoles aún no saben que padecen la enfermedad y tampoco reciben ningún tratamiento específico para la misma.

La EPOC es la cuarta causa de muerte en el mundo y, al igual que se espera que la prevalencia se incremente en los próximos 30 años, ocurrirá lo mismo con la mortalidad, por lo que la OMS estima que en 2030 será la tercera causa de muerte en el mundo, con más de 4,5 millones de fallecimientos al año por la EPOC y sus complicaciones. Asimismo, la EPOC

condiciona una importante pérdida de calidad de vida relacionada con la salud para nuestros pacientes, superada únicamente por la enfermedad coronaria.

1.3. EPOC y CP.

Como se ha expuesto previamente, tanto el CP como la EPOC son dos entidades que comparten una serie de características comunes. En ambas es característica una elevada mortalidad, con importante comorbilidad asociada. Además, ambas enfermedades tienen en común una serie de factores de riesgo tales como el tabaquismo, alteraciones genéticas, exposiciones ambientales y otras que cursan con inflamación. La EPOC es una comorbilidad muy frecuente en pacientes con CP, con una prevalencia muy variable y que oscila entre el 28 y el 40%. La evidencia de una asociación entre la EPOC y el desarrollo de CP se ha observado en estudios poblacionales, estudios de screening de CP y estudios de casos y controles, describiéndose un incremento en la incidencia y mortalidad del CP en pacientes con obstrucción al flujo aéreo. El infradiagnóstico de la EPOC es muy elevado en la mayoría de las series. También en aquellas con CP, donde algunos estudios han mostrado un diagnóstico previo de EPOC del 7,1% en pacientes con CP. La EPOC en pacientes con CP puede suponer ciertas limitaciones a la hora de iniciar un tratamiento para el tumor. Una de las consecuencias es que los pacientes sean inoperables, debido a una limitación funcional. Además, aumenta la frecuencia de todas las complicaciones postoperatorias, tales como la neumonía (10,1-16,2% tras la cirugía). Hay pocos estudios que hayan investigado el efecto de la EPOC en pacientes con formas avanzadas de CP. La presencia de EPOC no ha demostrado un empeoramiento del pronóstico en pacientes con quimio o inmunoterapia, ni tampoco con cambios en la calidad de vida.

1.3.2. Factores de riesgo para desarrollar enfermedad.

Sabemos que el CP y la EPOC presentan factores etiopatogénicos comunes, tales como la exposición al humo del tabaco (activo, pasivo o a través de otros dispositivos tales como el cigarrillo electrónico), exposición a carbón, biomasa y exposiciones ambientales o laborales, elementos de la dieta o incluso factores genéticos, como los niveles de alfa-1 antitripsina.

Asimismo, ambas entidades presentan factores de riesgo individuales. En el caso del CP, son factores de riesgo conocidos la exposición al gas radón, la existencia de antecedentes familiares y cierto grado de predisposición genética. En el caso de la EPOC, serían factores etiológicos la edad, el sexo, el envejecimiento pulmonar, problemas durante la gestación, nacimiento o exposiciones posteriores que puedan afectar al crecimiento pulmonar, las infecciones repetidas en la infancia o en la adolescencia y factores socioeconómicos, factores que, en su mayoría, no podemos modificar.

Por otra parte, como ya se ha dicho, la EPOC supone un factor de riesgo para el desarrollo de CP, independientemente de la exposición al tabaco, con un riesgo entre 4 y 6 veces superior de desarrollar CP que pacientes fumadores, pero con función pulmonar normal. Este riesgo parece incrementarse con la caída progresiva del volumen espiratorio forzado en el primer segundo (FEV_1), independientemente también de la historia tabáquica. Existen varias hipótesis que podrían justificar que la EPOC suponga un factor de riesgo para desarrollar CP, tales como la inflamación, el estrés oxidativo, alteraciones epigenéticas u otros elementos tales como los factores inducibles a la hipoxia (que juegan un papel relevante en el desarrollo de cáncer a través del control directo de la expresión de reguladores epigenéticos tales como las demetilasas de lisina), el VEGF (regulador de la angiogénesis), el factor de crecimiento epidermoide (EGF) y el factor de crecimiento transformante-beta (TGF-β).

La inflamación mantenida de cualquier tejido origina mecanismos de reparación que, en caso de perpetuarse pueden derivar en procesos neoformativos. Ese es también el caso de la vía aérea, cuya inflamación mantenida se postula como uno de los mecanismos fisiopatológicos que juega un papel clave en la amplificación de la respuesta mutagénica inicial del CP. Posiblemente, la inflamación persistente en la vía aérea de los pacientes con EPOC puede inducir alteraciones en el epitelio bronquial que favorezcan la carcinogénesis. Además, un exceso en la producción de radicales oxigenados y nitrogenados podría inducir modificaciones estructurales y funcionales en las células, así como las alteraciones epigenéticas van a desempeñar un papel en el desarrollo del CP.

1.4. Enfisema y CP.

El enfisema pulmonar es una lesión patológica definida por el aumento de la vía aérea distal a los bronquiolos terminales acompañada por una destrucción de la pared de dicha vía aérea. El enfisema puede estar presente en varios fenotipos de la EPOC, e incluso en fumadores sin obstrucción al flujo aéreo. El 47-76% de los pacientes con CP presenta enfisema pulmonar. Hasta el momento, existen conclusiones divergentes en los estudios disponibles que exploran la relación entre el CP y el enfisema, que pueden explicarse por el método de detección de enfisema y por los distintos métodos de evaluación de la TC (tomografía computarizada) torácica, observándose que el enfisema detectado visualmente por un radiólogo experto parece superior a la detección automática a la hora de establecerlo como un factor de riesgo para desarrollar CP, incluso independientemente de la presencia de obstrucción al flujo aéreo. No existe un criterio validado para cuantificar la gravedad del enfisema y, por lo tanto, tampoco disponemos de datos que nos permitan establecer una asociación clara entre la gravedad del enfisema y el desarrollo de CP.

Existen varios tipos de enfisema, aunque no hay evidencias claras acerca de su relación con el desarrollo de CP o con otros tipos de enfermedad. El enfisema centrolobulillar se definió

como una dilatación de la vía aérea centrada en el bronquiolo respiratorio; el enfisema paraseptal como cambios en los alveolos más distales adyacentes a la superficie pleural o a los septos interlobulillares; el panlobular como aquel distribuido por todo el lóbulo pulmonar; el cicatricial como aquel asentado sobre zonas en las que previamente ha existido algún tipo de proceso inflamatorio que ha condicionado cambios residuales en el tejido pulmonar; y las bullas se definieron como áreas localizadas de enfisema mayores al centímetro de diámetro.

El enfisema centrolobulillar se suele asociar a una edad más avanzada, más carga tabáquica y gravedad, mientras que el paraseptal afecta predominantemente a lóbulos superiores y se asocia con el sexo masculino, mayor edad y patología intersticial siendo, de hecho, el que se presenta con mayor frecuencia en los casos de la combinación enfisema-fibrosis. El enfisema paraseptal no suele ser clínicamente relevante hasta estar en fases avanzadas y no ha mostrado relación con el desarrollo de síntomas en la EPOC, con el grado de obstrucción o con la historia tabáquica. El enfisema panacinar es común en pacientes jóvenes, se asocia con menor IMC y una EPOC más severa.

1.5. Justificación de la investigación

La EPOC y el CP son enfermedades de alto impacto sanitario que comparten factores de riesgo comunes siendo el principal el tabaquismo. A pesar de los grandes avances que se han producido en el conocimiento de ambas enfermedades existen una serie de aspectos muy poco analizados hasta el momento, que podrían tener repercusión sobre el ámbito asistencial. La existencia de una asociación entre el CP y la EPOC es un aspecto en discusión y los datos disponibles sobre el nivel de infradiagnóstico de la EPOC en los pacientes con CP y su caracterización fenotípica y multidimensional es escasa o nula. Por ello consideramos pertinente y relevante el estudio de la interrelación de ambas enfermedades con tanto impacto con el fin de generar las bases científicas necesarias para conocer mejor la interrelación entre ambas patologías, pudiendo transferir los resultados de la investigación a la práctica clínica.

2. Métodos

El objetivo general del proyecto es estimar la prevalencia de EPOC y el grado de infradiagnóstico en pacientes con CP, así como evaluar el perfil clínico de pacientes con EPOC y CP y compararlo con otro grupo control de pacientes con EPOC sin CP, analizando su caracterización fenotípica y multidimensional, para una potencial utilidad en la detección precoz de CP en pacientes con EPOC o incluso pronóstica y en la toma de decisiones de tratamiento. Se establecieron los siguientes objetivos específicos:

1. Estimar la prevalencia de EPOC entre pacientes con diagnóstico de CP, así como el grado de infradiagnóstico en este grupo (pacientes no diagnosticados previamente en los que se detecta EPOC en la espirometría realizada dentro del estudio de CP).

2. Analizar, dentro de los pacientes con CP, las características clínicas diferenciales de los pacientes con EPOC concomitante.

3. Evaluar el perfil clínico de estos pacientes con EPOC y CP, y compararlo con otro grupo control de pacientes con EPOC sin CP, analizando su caracterización fenotípica y multidimensional.

4. Estudiar si existe una relación entre un tipo concreto de enfisema y la existencia de CP en pacientes con EPOC.

5. Comparar una serie de marcadores inflamatorios entre pacientes con EPOC y CP y pacientes con EPOC sin CP para poder proponer una hipótesis que ayude a establecer una posible detección precoz del CP en pacientes con EPOC.

3. Diseño

Inicialmente y, teniendo en cuenta la importancia de una potencial relación entre la EPOC, el enfisema y el desarrollo de CP, se realizó una revisión sistemática de la literatura para analizar la evidencia científica disponible sobre esta asociación, desarrollando posteriormente el proyecto de investigación que incluyó otros tres trabajos.

Para llevar a cabo esta tesis se diseñaron, por lo tanto, cuatro trabajos:

1. Una revisión sistemática, tal y como se ha reflejado en el párrafo superior.

2. Un estudio prospectivo de cohortes con fines descriptivos de la frecuencia y características fenotípicas de los pacientes diagnosticados sincrónicamente de EPOC y CP.

3. Un estudio observacional de casos y controles, siendo los casos pacientes con EPOC y CP y los controles, pacientes con EPOC sin CP. En este grupo de pacientes se analizaron de forma comparativa la caracterización fenotípica y el impacto de la EPOC mediante valoraciones clínicas, cuestionarios necesarios y la evaluación de la TC pulmonar.

4. Un estudio prospectivo de casos y controles en el que se compararon los niveles en sangre de los siguientes parámetros analíticos en tres grupos de pacientes (EPOC sin CP, CP sin EPOC y EPOC y CP): interleukinas 6 y 8 (IL-6 e IL-8), fibrinógeno, factor de necrosis tumoral (TNF)-α, proteína C reactiva (PCR), leucocitos, linfocitos, neutrófilos, ratio neutrófilos-linfocitos (NLR), plaquetas, volumen plaquetar medio (VPM), ratio plaquetas-linfocitos (PLR), A1AT, inmunoglobulina E (IgE), colesterol y bilirrubina.

Este proyecto cuenta con la valoración favorable del Comité Ético de Investigación Clínica de Galicia (expediente 2013/439), cuyo informe se adjunta en el Anexo. Todos los

pacientes firmaron el consentimiento informado. Los datos se incluyeron en una base de datos confidencial y anonimizada.

Para la realización de la revisión sistemática incluimos estudios de cohortes, de casos y controles, revisiones sistemáticas o metaanálisis, que incluyeran al menos 500 individuos. De acuerdo con los criterios diagnósticos de EPOC incluimos pacientes mayores de 35 años con un consumo acumulado de tabaco superior a los 10 años/paquete y con una espirometría obstructiva de forma irreversible. En cuanto al diagnóstico de enfisema, incluimos estudios con una evaluación cuantitativa o cualitativa del mismo mediante tomografía computarizada (TC). Solo se incluyeron estudios con confirmación histológica del diagnóstico de CP.

Posteriormente, se diseñó un estudio observacional de cohortes prospectivas y dos estudios de casos y controles de pacientes con CP, con EPOC y con EPOC y CP. En estos grupos de pacientes se analizaron de forma comparativa la caracterización fenotípica, el impacto de la EPOC mediante las valoraciones clínicas y cuestionarios necesarios y también la existencia de enfisema. También se compararon los niveles en sangre de un panel de 16 biomarcadores que se detallan más adelante.

El estudio de cohortes de pacientes con CP con o sin EPOC es un estudio multicéntrico que incluye a pacientes de dos hospitales: el Complexo Hospitalario Universitario de Vigo y el Complexo Hospitalario Universitario de Ourense. El segundo y el tercer estudio incluyen a pacientes del Complexo Hospitalario Universitario de Vigo. El Complexo Hospitalario Universitario de Vigo es un centro de tercer nivel que atiende a un área sanitaria de 450.000 habitantes, mientras que el Complexo Hospitalario Universitario de Ourense es un centro de segundo nivel que atiende a un área de 255.000 habitantes. El Servicio de Neumología del Complexo Hospitalario Universitario de Vigo realiza prácticamente todos los procedimientos y técnicas pulmonares y pleurales disponibles, contando con varias unidades acreditadas de máxima complejidad, e incluye una Unidad de Diagnóstico Rápido de Cáncer de Pulmón (UDRCP) como parte de un enfoque multidisciplinar iniciado por un sistema electrónico donde los radiólogos alertan a los neumólogos cuando hay una sospecha radiológica de CP. Esta unidad evalúa alrededor del 95% de todos los pacientes con CP en el área.

Se realizó un análisis descriptivo de todas las variables incluidas. Posteriormente, se realizaron análisis bivariantes para evaluar las diferencias entre grupos. Se empleó la t de Student para las variables cuantitativas y el test $\chi 2$ para las cualitativas. El límite de significación fue $p<0,05$. Las variables significativas en el análisis bivariante se incluyeron en un modelo de regresión logística, expresando los datos como OR con intervalos de confianza del 95%. Se empleó el método Kaplan-Meier para realizar las estimaciones de supervivencia. En el tercer subestudio se realizaron dos modelos de regresión logística multivariante, el primero ajustando

por edad y sexo y el segundo incluyendo también las variables significativas en el primero. Para ello, las variables cuantitativas se estratificaron en terciles para su inclusión en los modelos de regresión logística. Ello condujo al diseño de una variable de riesgo para cada paciente en base a los resultados de la regresión logística. Posteriormente, se desarrolló una curva ROC, para evaluar la sensibilidad, especificidad y valores predictivos de la variable de riesgo, teniendo en cuenta una prevalencia de CP en pacientes con EPOC del 25. El análisis se realizó con el programa SPSS 21.0 (IBM Corporation, Armonk, Nueva York).

4. Resultados

En la revisión sistemática "EPOC, enfisema y el desarrollo de cáncer de pulmón. Una revisión sistemática", se ha desarrollado una revisión de la literatura publicada para analizar sistemáticamente la evidencia científica disponible en la asociación entre EPOC, enfisema y CP, aplicando criterios de inclusión y exclusión predefinidos. Se incluyeron 11 estudios. Los resultados muestran que, tanto la EPOC como el enfisema, parecen aumentar el riesgo de desarrollar CP, siendo este riesgo mayor para los fumadores con un mayor consumo de tabaco. Estos resultados enfatizan la necesidad de que los médicos realicen espirometrías en los fumadores actuales y anteriores y en las pruebas de imagen pulmonar cuando sea necesario para identificar la EPOC y el enfisema y, por lo tanto, seleccionar pacientes con mayor riesgo de desarrollar CP.

En el artículo de cohortes "EPOC en pacientes con cáncer de pulmón: prevalencia, infradiagnóstico y caracterización clínica" se reclutaron 602 pacientes con CP, la mayoría hombres (77,9%), con una media de edad de 67 años. La prevalencia de EPOC entre los pacientes con CP fue del 51,5%, con un infradiagnóstico del 80%. Los pacientes con CP y EPOC eran mayores y la proporción de hombres era mayor en comparación con los pacientes con CP sin EPOC. Además, los pacientes con CP y EPOC tuvieron un índice de paquetes-año más alto, una mayor proporción de CP escamosos, una menor KCO y puntuaciones de Charlson más altas que los pacientes con CP sin EPOC. La supervivencia media de los pacientes con CP sin EPOC fue un 37% mayor que la de los pacientes con CP y EPOC (16 meses frente a 22 meses). Por lo tanto, se concluyó que la EPOC es prevalente entre los pacientes con CP, siendo una entidad altamente infradiagnosticada. Los pacientes con CP y EPOC son más escamosos, más comórbidos y tienen un KCO más bajo, por lo que se debe hacer un mayor esfuerzo en realizar un diagnóstico precoz de la EPOC, seleccionando pacientes con mayor riesgo de desarrollar cáncer de pulmón.

En el estudio de casos y controles "Influencia del tipo de enfisema en la relación entre la EPOC y el CP" se incluyeron 243 sujetos (169 casos con CP y EPOC y 74 controles con EPOC sin CP). Al comparar ambos grupos, el único factor significativamente diferente fue la presencia de enfisema paraseptal (solo o combinado) [OR=2,2 (IC95%1,1-4,3; p=0,03)]. De forma

secundaria, se analizaron las características del grupo de pacientes con enfisema paraseptal, siendo el adenocarcinoma pulmonar un tipo histológico más frecuente en este grupo que en otros tipos de enfisema (67,2% vs. 32,8%; p=0,03). Es por ello que los pacientes con EPOC y enfisema paraseptal podrían ser un grupo de riesgo para el desarrollo de CP, especialmente del subtipo adenocarcinoma.

En el estudio de casos y controles (pendiente de publicación) "Valor predictivo de una serie de marcadores inflamatorios en EPOC para el diagnóstico de CP" se incluyeron 280 pacientes, 109 casos (CP y EPOC), 83 controles (EPOC) y otros 88 pacientes con CP sin EPOC. No se observaron diferencias en la distribución por sexo, edad, IMC, tabaquismo, exposición ocupacional, función pulmonar, estadio o comorbilidad. Los pacientes con CP y EPOC tuvieron niveles significativamente mayores de neutrófilos [OR 1,00 (IC 95% 1,00-1,00); p=0,03] y A1AT [OR 1,02 (IC95% 1,01-1,03); p=0,003] y niveles de colesterol más bajos [OR 0,98 (IC95%: 0,97-0,99); p=0,009] que los controles con EPOC. Se desarrolló un score de riesgo combinando neutrófilos, A1AT y colesterol, logrando una sensibilidad del 80%, un valor predictivo negativo del 90,7% y un área bajo la curva de 0,78 (IC95% 0,71-0,86). Estos resultados muestran que los niveles elevados de neutrófilos y A1AT y los disminuidos de colesterol podrían predecir potencialmente el riesgo de pertenecer al grupo de pacientes con EPOC y CP.

5. Discusión

El mal pronóstico del CP, su elevada prevalencia entre pacientes con EPOC y la evidencia que postula a la EPOC como un factor de riesgo para el desarrollo de CP, hacen necesario elaborar estrategias con una potencial utilidad en la detección precoz del CP en pacientes con EPOC y/o enfisema. Por todo ello, resulta clave conocer mejor la interacción entre el CP y la EPOC, y también establecer si existe alguna relación entre el tipo de enfisema pulmonar y el desarrollo de CP. Además, ello tendría implicaciones pronósticas y terapéuticas e incluso de implementación de estrategias de cribado. En estos años se han publicado numerosos estudios que parecen mostrar la existencia de una relación entre el CP, la EPOC y el enfisema. Sin embargo, no existen estudios de caracterización fenotípica y multidimensional de los casos de EPOC con CP que nos puedan ayudar a elegir la terapia más adecuada y su pronóstico. Tampoco se ha estudiado la posibilidad de una relación entre distintos tipos de enfisema y la existencia de CP. Del mismo modo, existe escasa evidencia acerca del papel que representan algunos marcadores de inflamación en sangre, que podrían servir como herramientas de diagnóstico precoz, de posible cribado del CP, de determinación de gravedad, de evaluación de respuesta terapéutica y/o de toma de decisiones diagnósticas y terapéuticas en el subgrupo de pacientes con una EPOC de base. Como consecuencia de la escasa información disponible sobre la relación entre estas entidades, se decidió realizar este proyecto de investigación.

La mayoría de los pacientes incluidos en los estudios eran varones. Como se ha expuesto en la introducción, a lo largo de las últimas décadas, la proporción hombre/mujer con CP ha ido evolucionando de 10/1 a aproximadamente 4/1 en la actualidad, debido principalmente a la incorporación de la mujer al consumo de tabaco. En el grupo de CP y EPOC, el 88,7% de los casos eran varones, con una proporción 7/1. Ello se explica no solamente por la existencia de CP, sino también de la EPOC, al ser esta una enfermedad que afecta mayoritariamente a los varones. En el grupo de CP sin EPOC, la relación fue de 2/1, niveles inferiores a los descritos para el CP en la población general, lo que podría explicarse por una mayor proporción de mujeres dentro del grupo de los no fumadores, que se encuentran en su mayoría en el grupo que no padece EPOC.

La media de edad de nuestros pacientes (67 años) es ligeramente inferior a la descrita para el CP, si bien es cierto que en el subgrupo de pacientes con CP y EPOC sí es mayor. Quizá la edad descrita en la literatura se ve interferida por la presencia de EPOC, puesto que, si asumimos que la EPOC es un factor de riesgo para el desarrollo de CP, se precisaría de un tiempo de latencia previo al diagnóstico de la neoplasia. Ello explicaría el hecho de que los pacientes con CP sin EPOC sean más jóvenes.

En nuestros trabajos, al igual que en la población general, la mayoría de los diagnósticos de CP se realizan en estadios avanzados, lo que implica una baja supervivencia a los 5 años. El diagnóstico de CP (con o sin EPOC asociado) se realizó en estadios avanzados en más de la mitad de los casos, sin existir diferencias significativas entre tener o no una EPOC concomitante. Debido a que el tiempo de seguimiento de nuestro estudio de cohortes fue bajo (2 años), no pudimos extraer conclusiones definitivas sobre las implicaciones de este hecho en la supervivencia. Sin embargo, sí observamos que la mediana de supervivencia de pacientes con CP sin EPOC fue un 37% mayor que la de pacientes con EPOC, aunque no de forma significativa. No obstante, ambas medianas de supervivencia fueron bastante bajas (22 y 16 meses respectivamente).

La prevalencia de EPOC entre pacientes con CP fue del 51,5%, siendo EPOC ya conocidos el 28,4%. Esto muestra que la EPOC es una comorbilidad muy frecuente en pacientes con CP, con un marcado porcentaje de infradiagnóstico: un 71,6%, con niveles similares a los que podemos encontrar en la población general. Esto significa que, a pesar de la disponibilidad de guías nacionales e internacionales, la EPOC sigue siendo una entidad con un alto grado de infradiagnóstico, también en pacientes con CP. Ello puede suponer peor respuesta al tratamiento en aquellos pacientes con CP y EPOC, debido a las demoras en el diagnóstico y a la influencia que tiene la EPOC a la hora de condicionar la evolución y las opciones terapéuticas en estos pacientes.

La práctica totalidad (98%) de los pacientes con EPOC (con o sin CP) presentaban algún tipo de exposición previa al tabaco, siendo casi la mitad de los pacientes fumadores activos. Estos

resultados eran esperables, ya que el tabaquismo es prácticamente una condición necesaria para poder diagnosticar a un paciente de EPOC, salvo en aquellos casos con otro tipo de exposiciones (en nuestro caso, exposición al humo de biomasa). Más del 70% de los pacientes con CP sin EPOC había presentado algún tipo de exposición al humo de tabaco, siendo el 45,7% de los casos aún fumadores activos. Esto apoya claramente la evidencia que postula al tabaquismo como principal factor de riesgo para ambas enfermedades.

En los estudios, los pacientes eran frecuentemente EPOC leves y poco exacerbadores (en el estudio de cohortes, el 73,9% eran GOLD I-II y el 76,9% GOLD A-B, con un 90,3% de no exacerbadores; mientras que, en los estudios de casos y controles, el 69,8% eran GOLD I-II y el 90% GOLD A-B, con un 90,1% de no exacerbadores). Estos datos resultan relevantes, debido a que éste es el grupo de pacientes con EPOC que más nos interesa caracterizar, dado que su situación funcional puede permitir que se beneficien de estrategias diagnósticas, de evaluación de extensión y terapéuticas más agresivas frente a su patología oncológica. Además, hay evidencia que apunta a que el riesgo de desarrollar CP y de fallecer por él es mayor en pacientes con EPOC GOLD I-II, mientras que los pacientes con una EPOC más avanzada tienen mayor probabilidad de fallecer por la propia EPOC.

El adenocarcinoma fue el tipo histológico más frecuente de forma global en todos los estudios incluidos en esta tesis. Ello puede estar relacionado con diversos factores, tales como los cambios en las características de los cigarrillos (con filtro y bajos en nicotina), los cambios en la clasificación del adenocarcinoma (actualmente se clasifica como adenocarcinoma al carcinoma bronquiolo-alveolar), el aumento de diagnósticos casuales (al ser el adenocarcinoma un tumor más periférico y que tarda más en producir sintomatología) y al incremento de mujeres con CP, debido a su mayor susceptibilidad por factores genéticos, hormonales, y mutacionales, con un mayor riesgo de tener mutado el receptor de crecimiento epidérmico (EGFR).

El subgrupo de pacientes con CP y EPOC presentaban más frecuentemente carcinoma escamoso y CPM, cuando se compararon con los pacientes con CP sin EPOC. Además, encontramos que el carcinoma escamoso era el diagnóstico más frecuente en estadios localizados, mientras que en estadios avanzados el tipo histológico más frecuente fue el CPM. Ambos tipos histológicos se han asociado con el tabaquismo, con mayor frecuencia que en el caso del adenocarcinoma. Además, la presencia de carcinoma escamoso se asoció más significativamente con la presencia de enfisema, y en nuestra serie, los pacientes con CP y EPOC concomitante tenían una DLCO más baja, lo que podría indicar la existencia de un enfisema asociado y relacionarse así con una mayor prevalencia de carcinoma escamoso.

Los pacientes con CP y EPOC tenían más comorbilidades medidas por el índice de Charlson que los pacientes con CP sin EPOC, lo que se podría explicar por varios factores. Los

casos con CP y EPOC presentaban una mayor prevalencia de tabaquismo, pudiendo implicar la presencia de procesos inflamatorios crónicos que diesen lugar al desarrollo de mayor variedad de comorbilidades. Además, se sabe que además de la inflamación sistémica existen otros mecanismos que pueden influir en la coexistencia de EPOC con otras comorbilidades cardíacas y metabólicas, tales como la senescencia celular o el acortamiento telomérico.

Los pacientes con CP y EPOC eran más mayores y más delgados que los pacientes con EPOC sin CP. La mayor edad podría deberse al tiempo de latencia necesario para que la EPOC pueda dar lugar al desarrollo de CP, mientras que un IMC inferior podría estar relacionado con el hecho de que la mayoría de los casos eran pacientes no exacerbadores con enfisema.

Como ya se ha explicado previamente, la evidencia disponible acerca de la asociación entre la presencia de enfisema y el desarrollo de CP es débil, aunque sí que parece claro que la evaluación objetiva por parte de radiólogos especializados de la existencia de enfisema puede correlacionarse mejor con el desarrollo de CP que su detección por medio de sistemas automáticos. En nuestro trabajo no hemos encontrado una asociación significativa entre la existencia de enfisema (considerando conjuntamente todos los subtipos) y la presencia de CP, a pesar de haber realizado la evaluación de este enfisema de forma semicuantitativa por parte de cuatro radiólogas experimentadas. No obstante, en la literatura disponible hasta la fecha, no existen datos que analicen por separado los distintos tipos de enfisema, lo que podría suponer que la distribución entre formas de enfisema dentro de cada estudio sea heterogénea y que ello pueda contribuir por lo tanto a la disparidad de los resultados. Como se explica a continuación, sí encontramos una asociación entre un subtipo concreto de enfisema y la presencia de CP.

El segundo subestudio se centró en analizar la existencia de una relación entre un tipo en concreto de enfisema y la existencia de CP. Se observó una asociación entre el enfisema paraseptal (solo o combinado) y la presencia de CP en pacientes con EPOC. Se sabe que el enfisema paraseptal afecta predominantemente a lóbulos superiores, algo que también se observa en el presente trabajo. Es un tipo de enfisema que no suele ser clínicamente relevante hasta encontrarse en fases avanzadas, no habiendo demostrado relación con el desarrollo de síntomas en la EPOC, tampoco con el grado de obstrucción al flujo aéreo, ni con la historia tabáquica. En el estudio del enfisema, se realizó un análisis por subgrupos comparando las características de los pacientes con enfisema paraseptal con los de los otros tipos de enfisema, objetivando una mayor prevalencia de adenocarcinoma, lo que podría estar en relación con que se trata de un tumor periférico y que, al igual que en el caso del enfisema paraseptal, presenta manifestaciones clínicas más tardías.

En el tercer estudio se analizó un panel de 16 biomarcadores en tres grupos de pacientes: EPOC, CP y CP y EPOC. Los resultados de este estudio muestran que los pacientes con EPOC

que también tienen CP presentan niveles mayores de neutrófilos y A1AT e inferiores de colesterol. Los neutrófilos promueven la angiogénesis al secretar factores proangiogénicos. Además, intervienen en las rutas del factor de crecimiento epidérmico (EGFR), el factor de crecimiento transformante-β1 (TGF-β1) y factores de crecimiento derivados de plaquetas, contribuyendo así a la génesis tumoral. Se sabe que los recuentos de neutrófilos son un indicador independiente de mal pronóstico en pacientes con CP, mientras que los recuentos bajos de neutrófilos están asociados con una mayor supervivencia. La mayoría de los datos que relacionan la proteína A1AT con la EPOC o el CP se centran en su déficit. Sin embargo, su papel como marcador inflamatorio cuando se encuentra elevada no ha sido estudiado en este contexto. Por otra parte, aunque se necesitan más estudios para establecer si existe una asociación entre el riesgo A1AT y CP, hay evidencia de que A1AT promueve la metástasis del adenocarcinoma de pulmón. Aunque la hiperlipidemia es un factor de mal pronóstico en pacientes con cáncer de estómago y próstata, hay pocos estudios evaluando su papel en el CP. En un trabajo reciente, los niveles de HDL, LDL y colesterol total fueron menores en los pacientes con CP en comparación con los controles sanos, aunque solo los niveles de HDL fueron pronósticos significativos. En el estudio de los biomarcadores, además, elaboramos una escala de riesgo para predecir qué pacientes con EPOC tenían más riesgo de pertenecer al grupo de los casos (pacientes con EPOC y CP), logrando una alta sensibilidad y VPP. De hecho, el área bajo la curva es cercana al 0,80 y, por lo tanto, solo el 20% de los pacientes que usan esta puntuación se clasificaría incorrectamente. Por todo ello, A1AT, neutrófilos y colesterol se presentan como parámetros con potencial utilidad diagnóstica en el estudio de un posible CP en pacientes con EPOC. No obstante, aunque se trata de marcadores sensibles, no son específicos ni de EPOC, ni de CP, por lo que nuestros hallazgos sientan las bases para realizar más estudios que nos permitan seleccionar a aquellos sujetos con EPOC con una mayor probabilidad de beneficiarse del cribado por tomografía computarizada, así como poder seleccionar nódulos con mayor riesgo de ser malignos.

Los resultados mostrados en los trabajos incluidos en esta tesis forman parte de un proyecto multicéntrico nacional, incluido en el Programa Integrado de Investigación (PII) de Oncología Torácica de la Sociedad Española de Patología Respiratoria (SEPAR). Ello ha permitido desarrollar los cuatro artículos que constituyen esta tesis (la revisión sistemática, el estudio de cohortes y los dos estudios de casos y controles).

Los dos hallazgos más novedosos alcanzados en los trabajos que incluye esta tesis son que el enfisema paraseptal en pacientes con EPOC es más frecuente en el subgrupo de pacientes que además presentan CP, especialmente dentro del subgrupo de los adenocarcinomas, y que los niveles elevados de A1AT y de neutrófilos y los disminuidos de colesterol, se asocian con una mayor probabilidad de presentar un CP en pacientes con EPOC. De hecho, el estudio de los

biomarcadores nos ha permitido desarrollar una escala de riesgo que ha mostrado una elevada sensibilidad y valor predictivo negativo, con un área bajo la curva (AUC) cercana a 0,80.

Teniendo en cuenta estos resultados sobre el enfisema paraseptal y los biomarcadores sanguíneos, este proyecto se intentará continuar con varios trabajos multicéntricos a nivel nacional. Estos estudios se diseñarán para validar prospectivamente nuestros resultados, con el objetivo de poder plantear una escala combinada de parámetros clínicos, exposiciones de riesgo, función pulmonar, tipo de enfisema y marcadores en sangre, que permita seleccionar a aquellos pacientes con EPOC susceptibles de ser la población diana en estrategias de cribado de CP. Como objetivo secundario, se pretende modificar las escalas predictoras de malignidad en el estudio de nódulos pulmonares y otras lesiones sospechosas de CP en pacientes con EPOC.

6. Conclusiones

1. Según la literatura analizada en nuestra revisión sistemática, tanto la EPOC como el enfisema incrementan el riesgo de desarrollar CP, siendo este mayor para fumadores y aumentando a medida crece el consumo de tabaco. Estas entidades comparten varios mecanismos etiopatogénicos subyacentes.
2. En el estudio multicéntrico de cohortes, se ha podido constatar que la EPOC es una enfermedad altamente infradiagnosticada, también entre pacientes con CP. Los análisis realizados en este trabajo y en la revisión sistemática enfatizan la necesidad de realizar espirometrías en pacientes fumadores activos y en exfumadores, así como pruebas de imagen en aquellos casos en los que estén identificados, para poder diagnosticar correcta y precozmente la EPOC y el enfisema y así poder seleccionar pacientes con un riesgo aumentado de desarrollar CP.
3. Los pacientes con CP y EPOC presentan más frecuentemente carcinomas escamosos y menor DLCO que los pacientes con CP sin EPOC. Esto sugiere una relación entre el carcinoma escamoso, el tabaquismo y la presencia de enfisema.
4. Los pacientes con CP y EPOC tienen más comorbilidades que los pacientes con CP sin EPOC, lo que podría estar relacionado con la elevada prevalencia de tabaquismo en estos pacientes, además de con la propia EPOC.
5. El enfisema paraseptal en pacientes con EPOC es más frecuente en aquellos casos que también tienen CP. Además, los pacientes con enfisema paraseptal tienen una mayor proporción de casos de adenocarcinoma que otros tipos de enfisema. Por lo tanto, los pacientes con EPOC y enfisema paraseptal podrían ser un grupo de riesgo para el desarrollo de CP, especialmente del subtipo adenocarcinoma.
6. Los pacientes con EPOC que también padecen CP tienen niveles más altos de A1AT y neutrófilos y más bajos de colesterol. Estos marcadores parecen estar más relacionados con la presencia de CP que con la propia EPOC, ya que están aumentados en pacientes con CP sin EPOC.

Por otra parte, en pacientes con CP y EPOC en estadio localizado, el A1AT sigue siendo significativamente mayor. Además, la combinación de A1AT y neutrófilos presenta una alta sensibilidad y VPN, por lo que podrá ser una herramienta útil para identificar pacientes con CP y EPOC. Sin embargo, aunque son sensibles, estos marcadores no son específicos de CP, y se necesitan más estudios para que estos biomarcadores puedan utilizarse en la práctica clínica con el objetivo de seleccionar a aquellos sujetos con EPOC con mayor probabilidad de beneficiarse del cribado por TC, o para seleccionar aquellos nódulos u otras lesiones con mayor riesgo de malignidad.